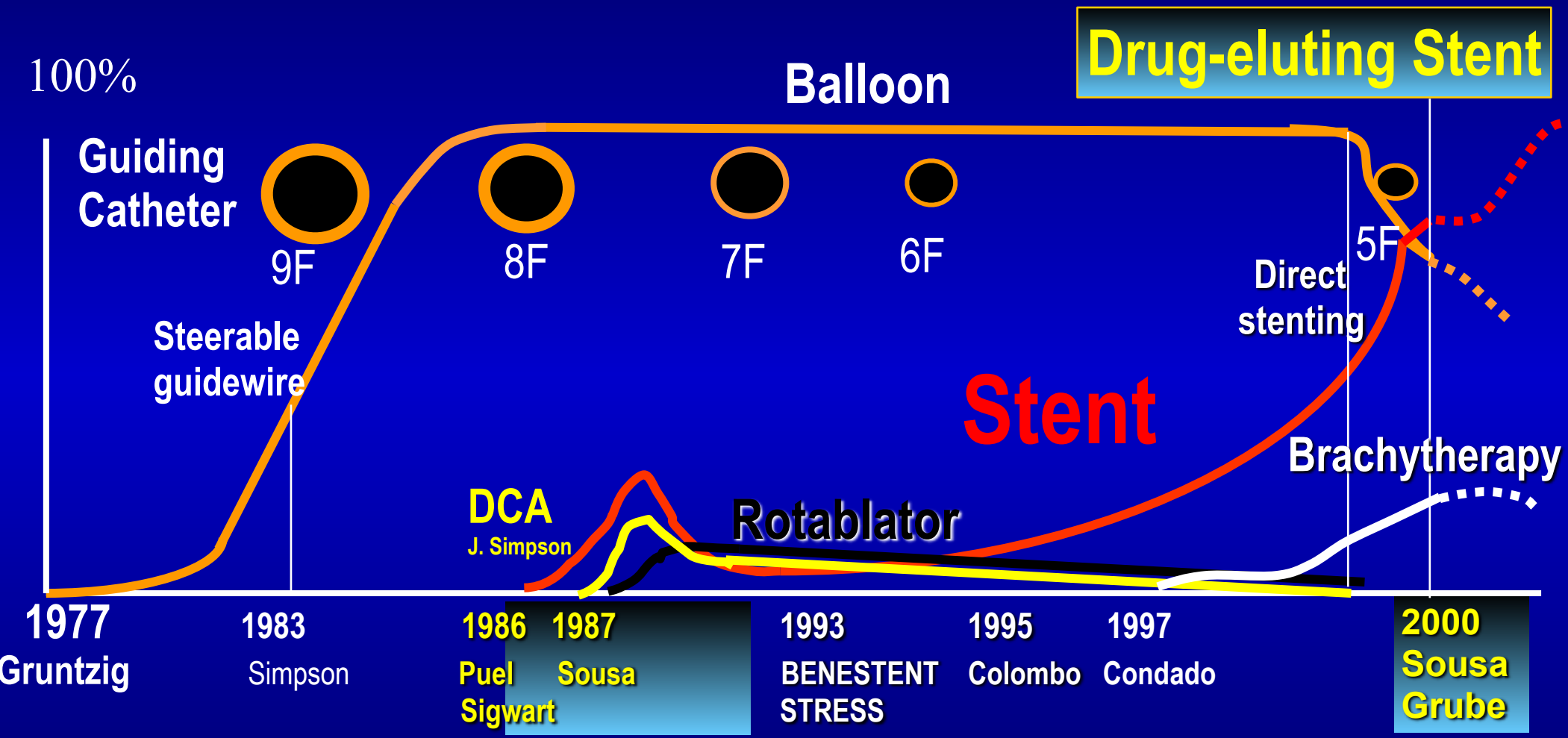
Novel Antiplatelet Agents

Dominick J. Angiolillo, MD, PhD, FACC, FESC
Director of Cardiovascular Research
Assistant Professor of Medicine

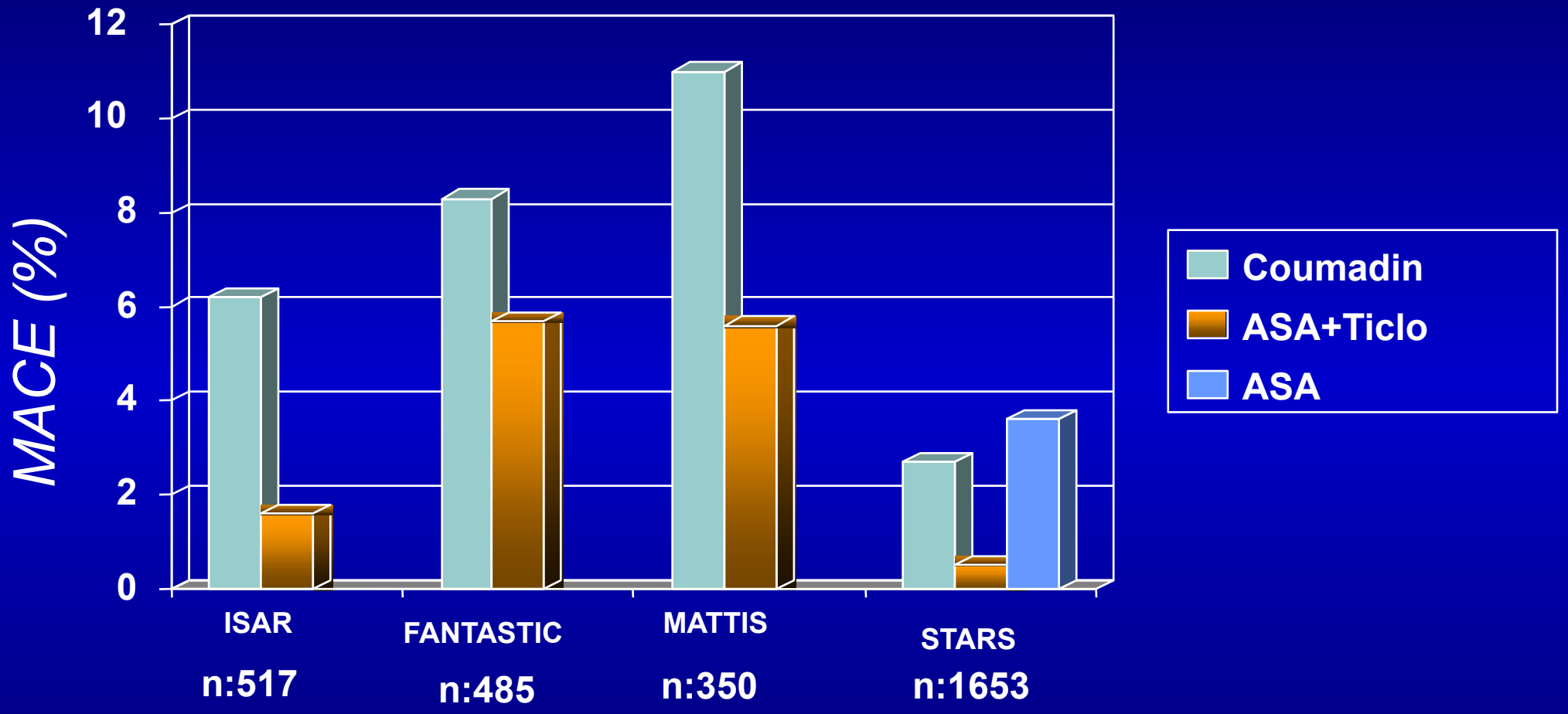
How did we get here?...

Charles Dotter – *Peripheral Angioplasty. Circulation 1964.*



Modified from Michel Bertrand

Ticlopidine during PCI with use of Coronary Stents



- *Schomig et al, N Engl J Med 1996*
- *Urban et al, Circulation 1998*
- *Bertrand et al, Circulation 1998*
- *Leon et al, Circulation 1998*

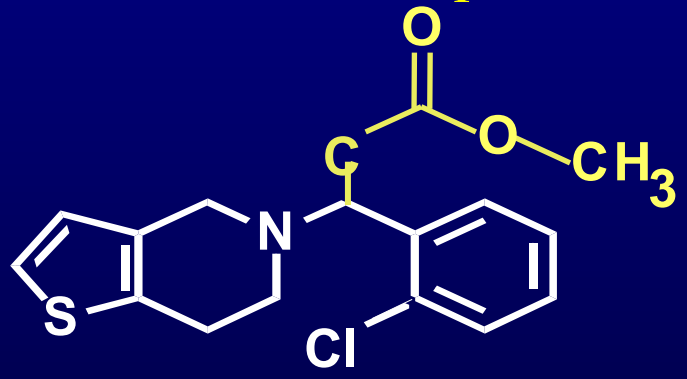
The Thienopyridine Family

Ticlopidine

(1st generation)

- $P2Y_{12}$ ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting
- Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc
- Delayed time frame to achieve full antiplatelet effects

Solution to these problems:

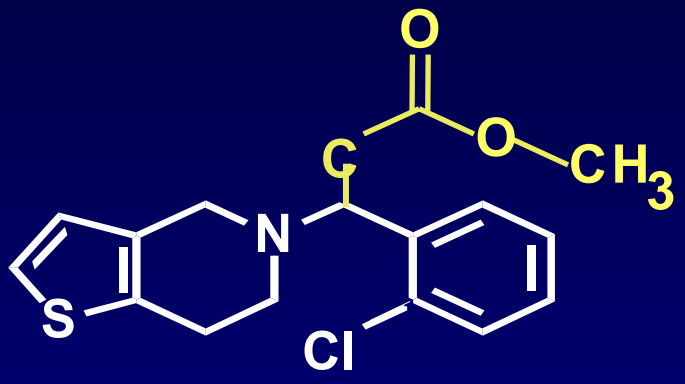


Clopidogrel

(2nd generation)

- **Better Safety profile - Fewer side effects**
  (CLASSICS trial. Bertrand NE *et al. Circulation* 2000; 102: 624–9).
- **Rapid onset of action with a loading dose**
  (Cadroy Y *et al. Circulation*. 2000;101:2823-28).
- **Better clinical outcomes**
  (Bhatt DL *et al. J Am Coll Cardiol* 2002; 39: 9–14.).

The Thienopyridine Family



Clopidogrel

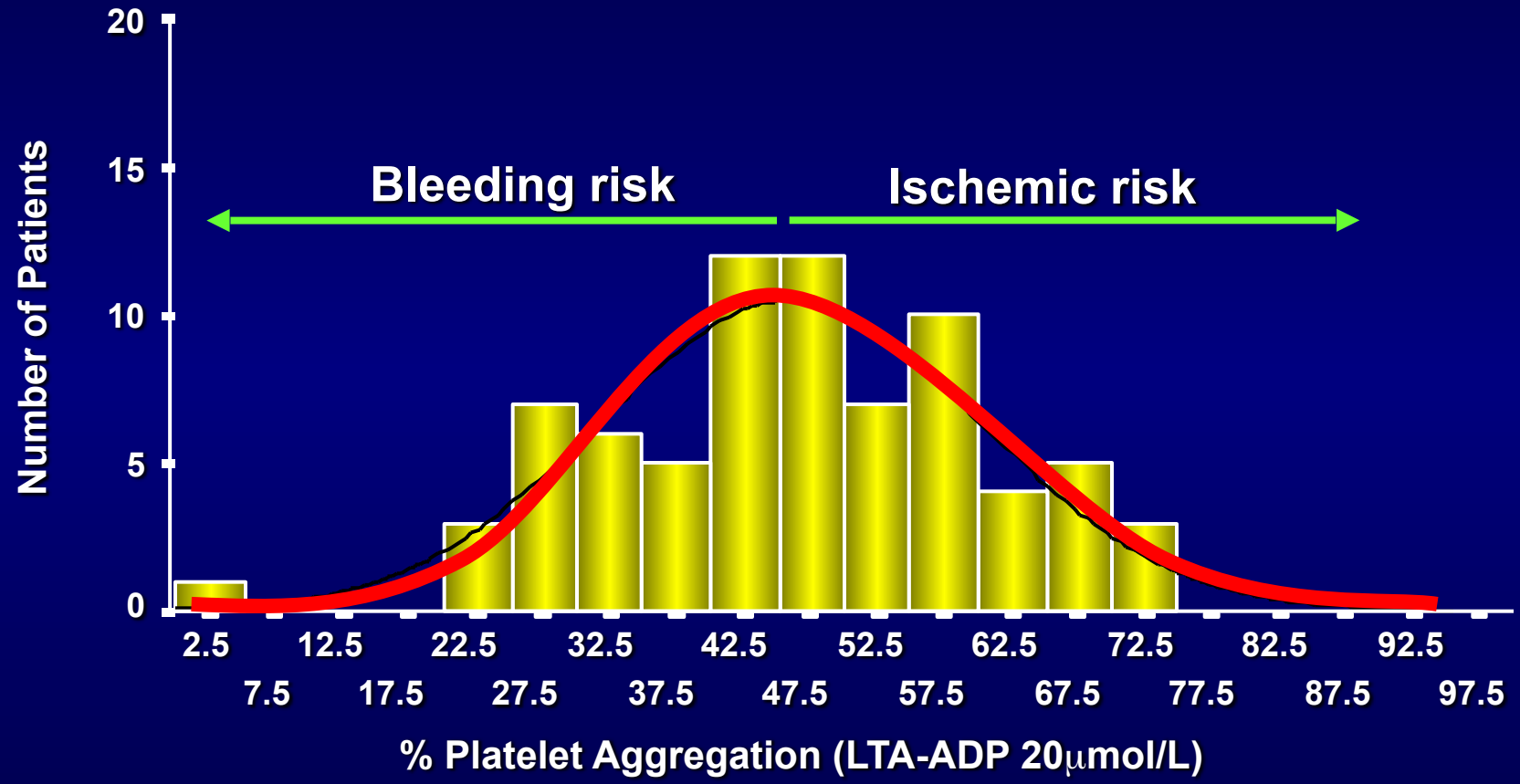
(2nd generation)

- Better Safety profile - Fewer side effects
- Rapid onset of action with a loading dose of 300 mg
- Better clinical outcomes

1) Irreversible platelet inhibitor **2) Interindividual response variability**

- bleeding risk in CABG
- full antiplatelet effects not always so rapid
- level of inhibition not always so high
- clopidogrel resistance

Individual Response Variability to Dual Antiplatelet Therapy in the *Steady State Phase* of Treatment



Adapted from Angiolillo DJ et al. *Am J Cardiol.* 2006;97:38-43.

Clinical Relevance of Clopidogrel Non-responsiveness

Post-Stent Ischemic Events and Periprocedural Infarction

	N	Functional Parameter	Clinical Relevance
Matezky et al. Circulation 2004	60	↑ platelet aggregation (4th quartile)	Post-primary PCI ischemic events (6 months)
Gurbel et al. JACC 2005	192	↑ periprocedrual platelet aggregation	Post-PCI ischemic events (6 months)
Gurbel et al. Circulation 2005	120	↑ periprocedrual platelet aggregation	Myonecrosis and inflammation marker release
Cuisset et al. J Thromb Haemost 2006	106	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Lev et al. JACC 2006	120	↑ clopidogrel/aspirin-resistant patients	Post PCI-myonecrosis
Cuisset et al. JACC 2006	292	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Hocholzer et al. JACC 2006	802	↑ platelet aggregation (3rd & 4th quartiles)	Post-PCI ischemic events (30 days)
Geisler et al. Eur Heart J 2006	379	↓ platelet inhibition	Post-PCI ischemic events (3 months)
Bliden et al. JACC 2007	100	↑ platelet aggregation	Post-PCI ischemic events (12 months)
Angiolillo et al. JACC 2007	173	↑ platelet aggregation (4th quartile)	Ischemic events (24 months)

adapted from Angiolillo DJ et al. *Am J Cardiov Drugs.* 2007.

Clinical Relevance of Clopidogrel Non-responsiveness

Stent Thrombosis

	N	Functional Parameter	Clinical Relevance
Mueller et al. Thromb Haemost 2003	105	↓inhibition of platelet aggregation	Stent thrombosis
Barragan et al. CCI 2003	36	↑$P2Y_{12}$ reactivity ratio (VASP-levels)	Stent thrombosis
Gurbel et al. JACC 2005	120	↑$P2Y_{12}$ reactivity ratio; ↑platelet aggregation; ↑stimulated GPIIb/IIIa expression	Stent thrombosis
Ajzenberg et al. JACC 2005	49	↑shear-induced platelet aggregation	Stent thrombosis
Buonamici et al JACC 2007	804	↑ platelet aggregation	Stent thrombosis

adapted from Angiolillo DJ et al. *Am J Cardiov Drugs.* 2007.

Ideal ADP $P2Y_{12}$ receptor antagonist

- Rapid onset
- High level of inhibition
- No resistance
- Reversible

Novel ADP $P2Y_{12}$ receptor antagonist

Prasugrel

AZD6140

Cangrelor

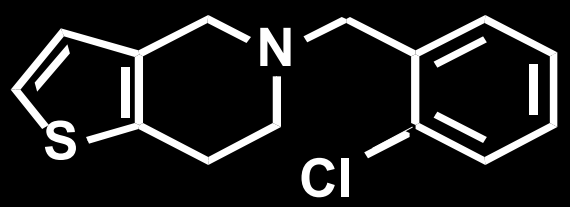
Novel ADP $P2Y_{12}$ receptor antagonist

Prasugrel

AZD6140

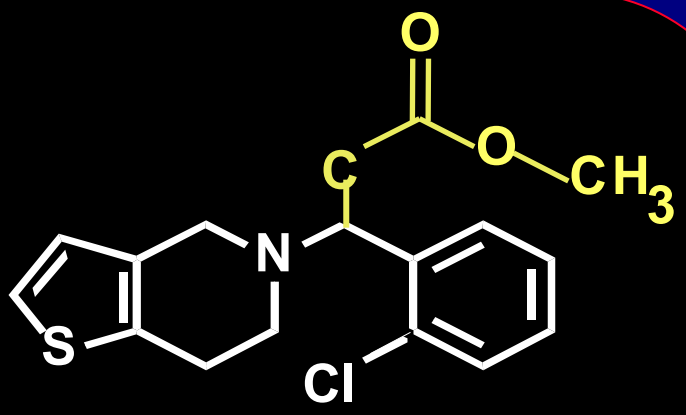
Cangrelor

The Thienopyridine Family



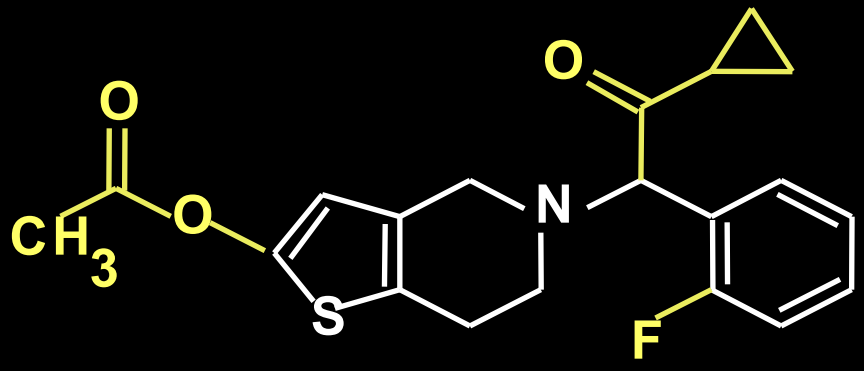
Ticlopidine

(1st generation)



Clopidogrel

(2nd generation)



Prasugrel (CS-747) (LY640315)

(3rd generation)

Sem Vasc Med 3:113, 2003

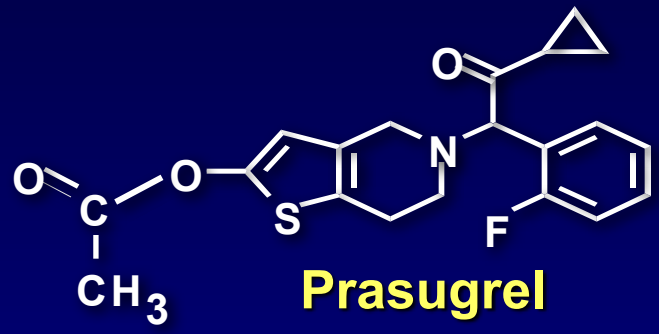
Sankyo Ann Report 51:1,1999

Active Metabolite Formation

Clopidogrel

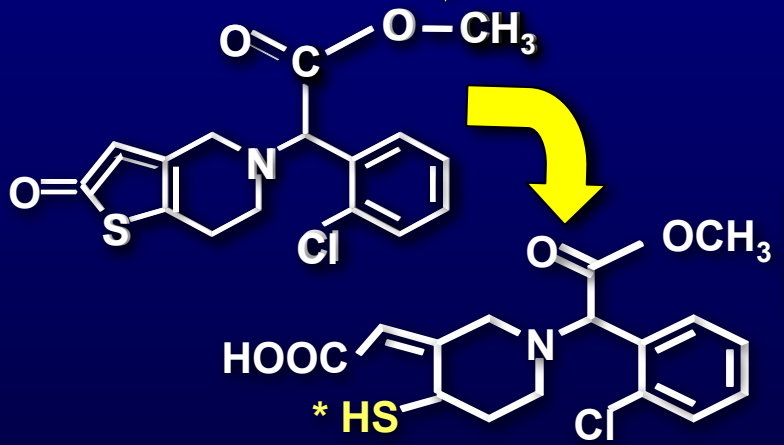
Pro-drug

Pre-hepatic metabolism
Esterases in blood
(? Small Intestine)

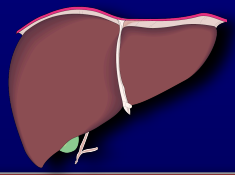


Prasugrel

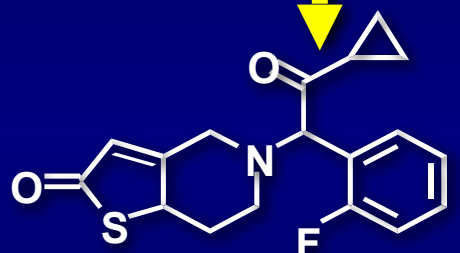
85% Inactive Metabolites
Esterases in blood

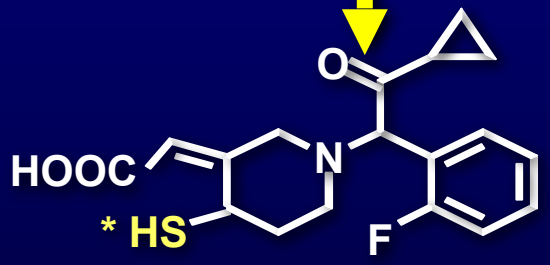


Active Metabolite



Hepatic Metabolism
Cytochrome P450

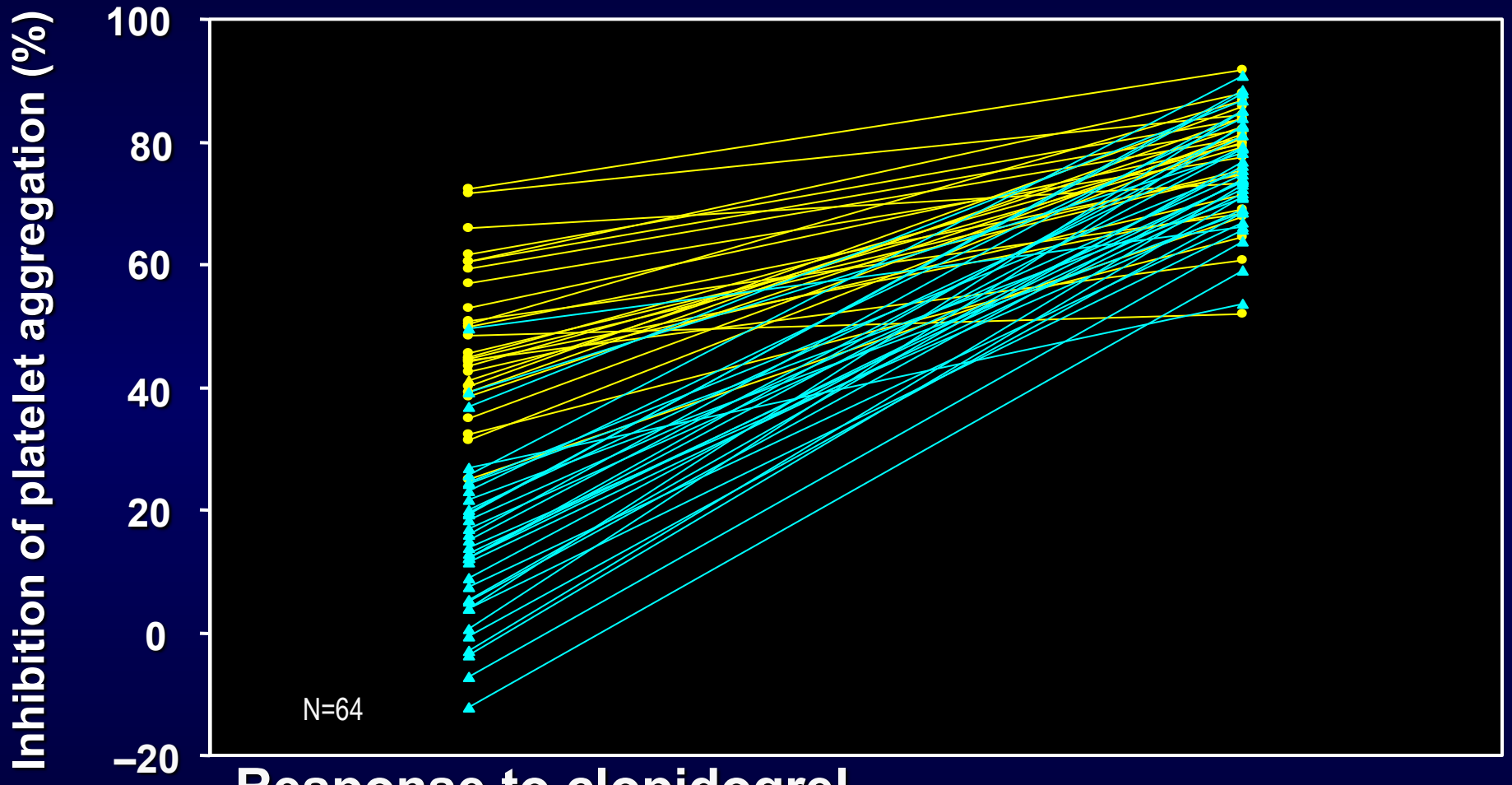




Active Metabolite

Healthy volunteer crossover study

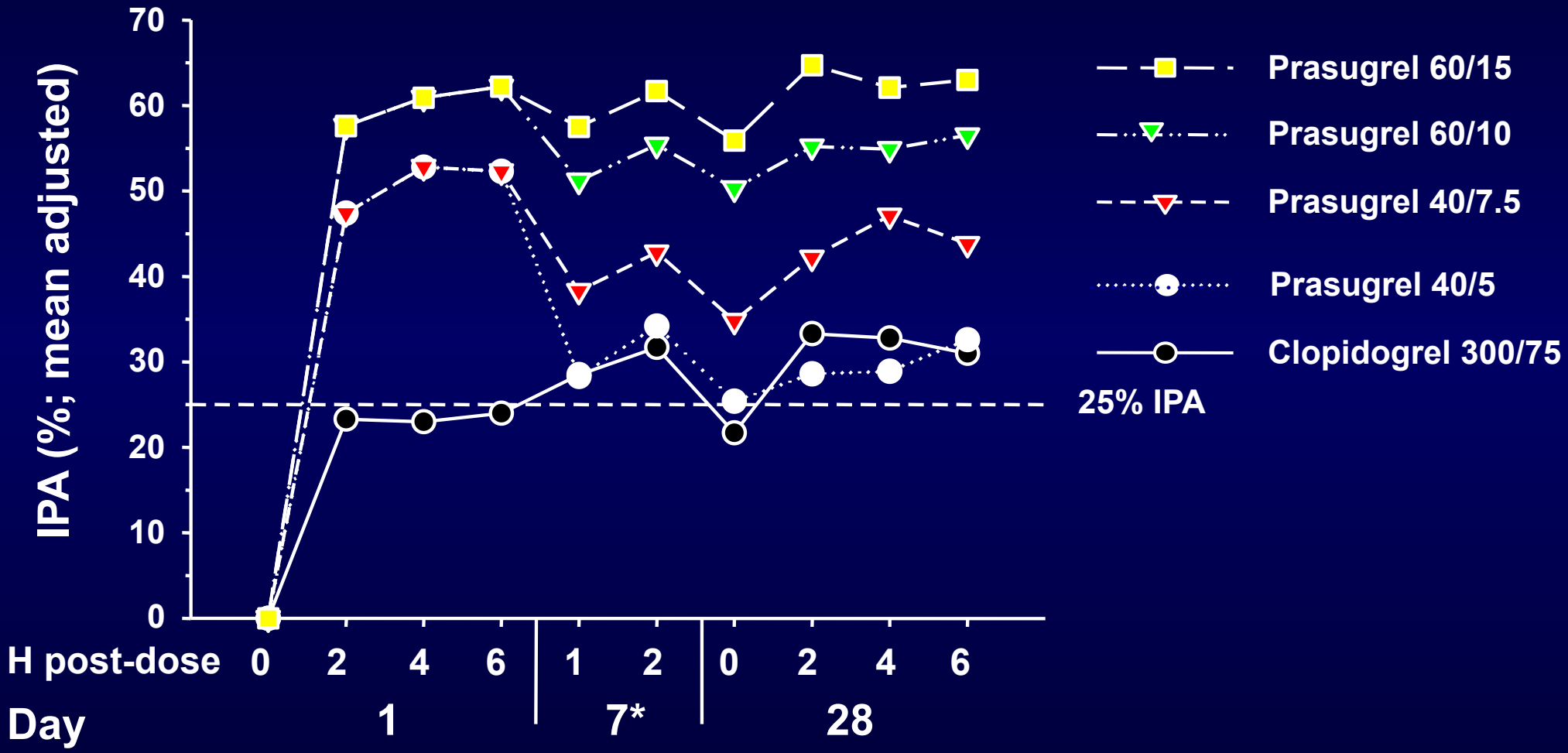
IPA (20 μM ADP) at 24 hours



Brandt J et al. AHJ 2006

Prasugrel vs. Clopidogrel: Stable CAD

Inhibition of Platelet Aggregation (28 days; 20 μM ADP)



Jernberg T et al. Eur Heart J 2006; 27: 1166-73.

STUDY DESIGN

PCI with stenting (N=900)

Study Drug in lab; Stratify for GP IIb/IIIa

PRASUGREL	PRASUGREL	PRASUGREL	CLOPIDOGREL
LD 40 mg	LD 60 mg	LD 60 mg	LD 300 mg
MD 7.5 mg	MD 10 mg	MD 15 mg	MD 75 mg
N=200	N=200	N=250	N=250

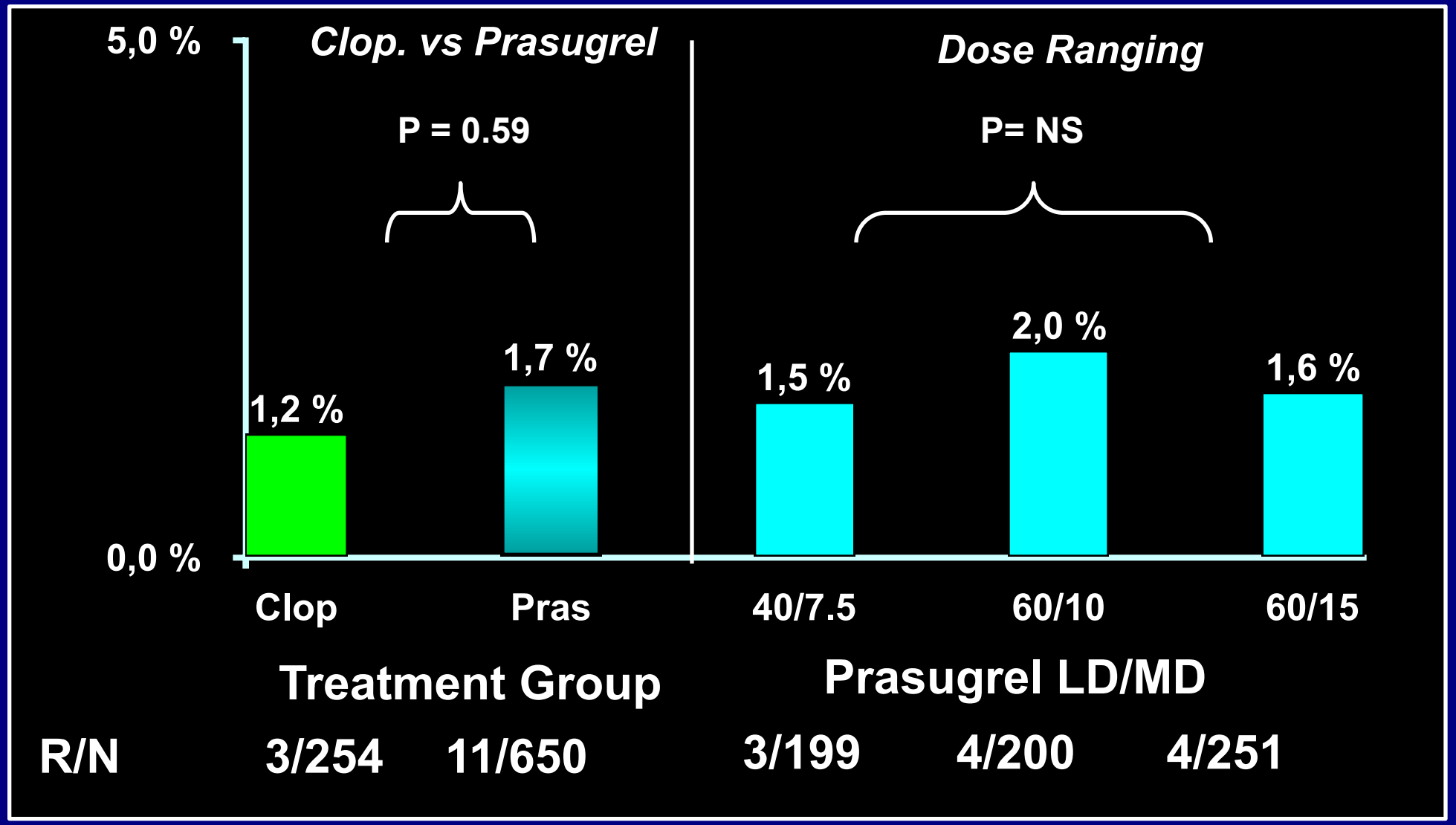
Maintenance Rx for 30 days

1º endpoint: Significant (non-CABG) bleeding through 30 D

2º endpoints: MACE through 30 D, Major Bleeding, Component Clinical Endpoints

Wiviott SD et al. Circulation 2005; 111: 3366-73.

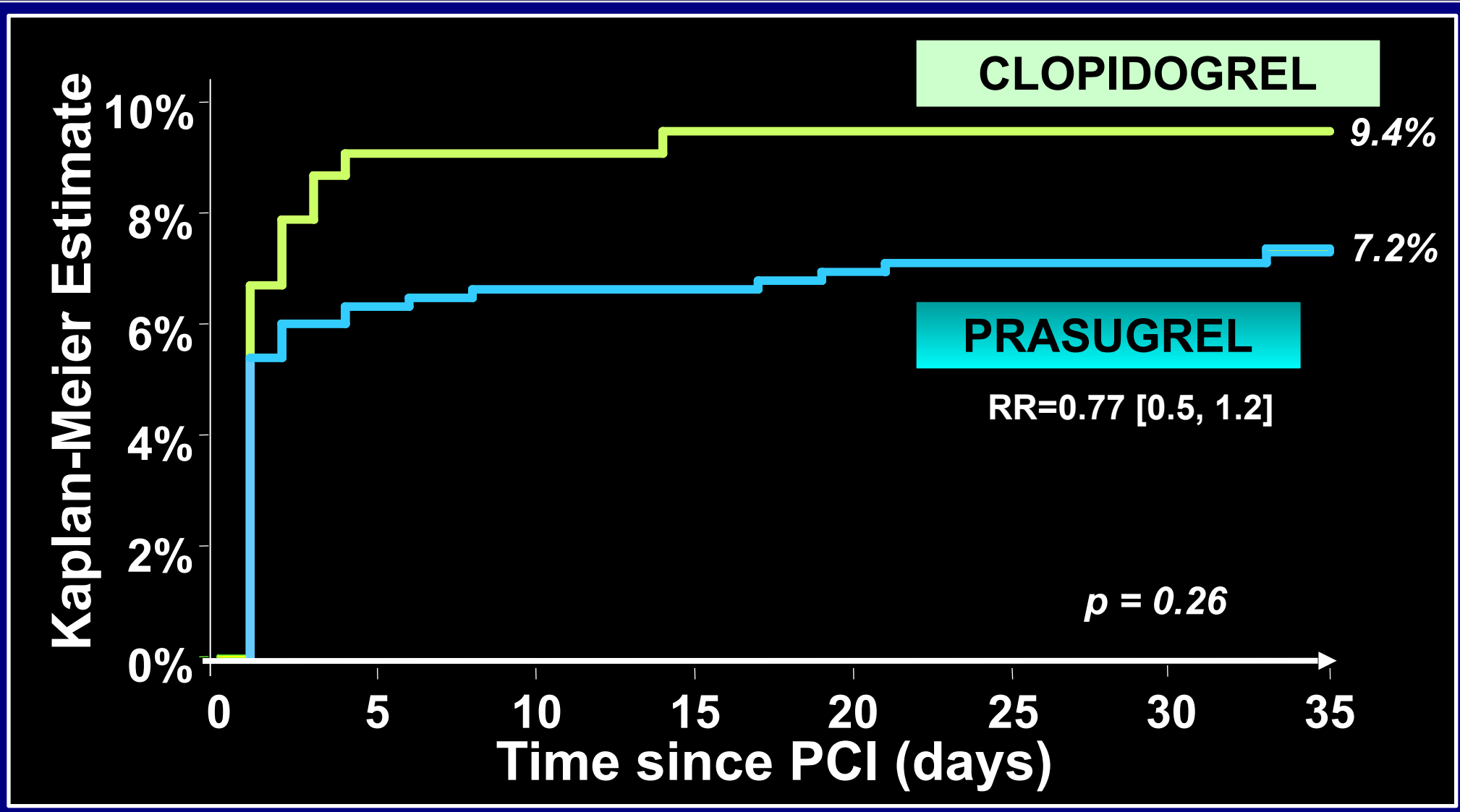
1º EP: Significant Non-CABG Bleeding 30 D



Wiviott SD et al. Circulation 2005; 111: 3366-73.

MACE: Time to Event

Death, MI, CTVT, Stroke, and Recurrent Ischemia



Wiviott SD et al. Circulation 2005; 111: 3366-73.

TRITON TIMI-38

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,600

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

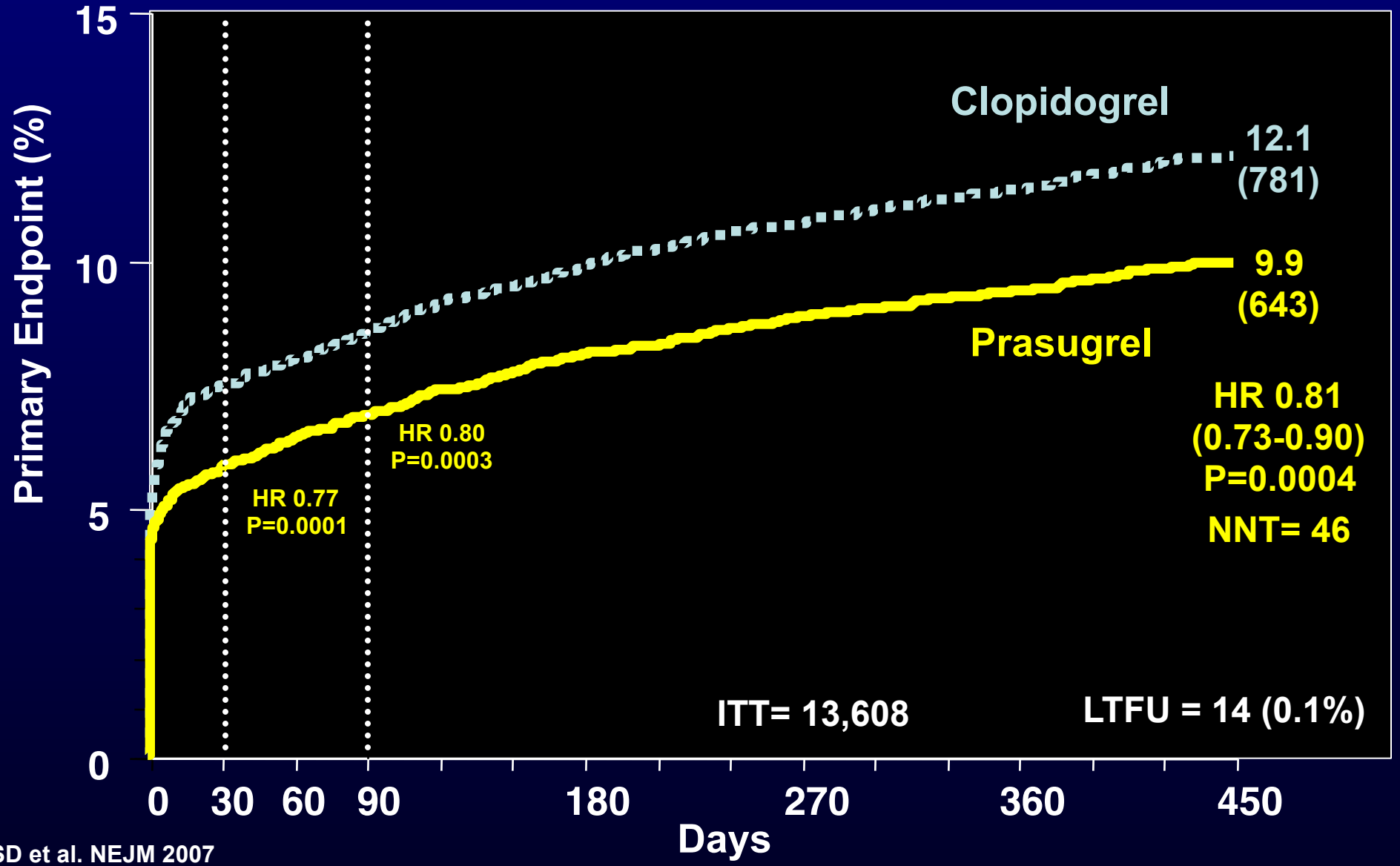
PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Rehosp-Rec Isch CV death, MI, UTVR
	Stent Thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key Substudies:	Pharmacokinetic, Genomic

TRÎTON TIMI·38

Primary Endpoint
CV Death,MI,Stroke



Wiviott SD et al. NEJM 2007

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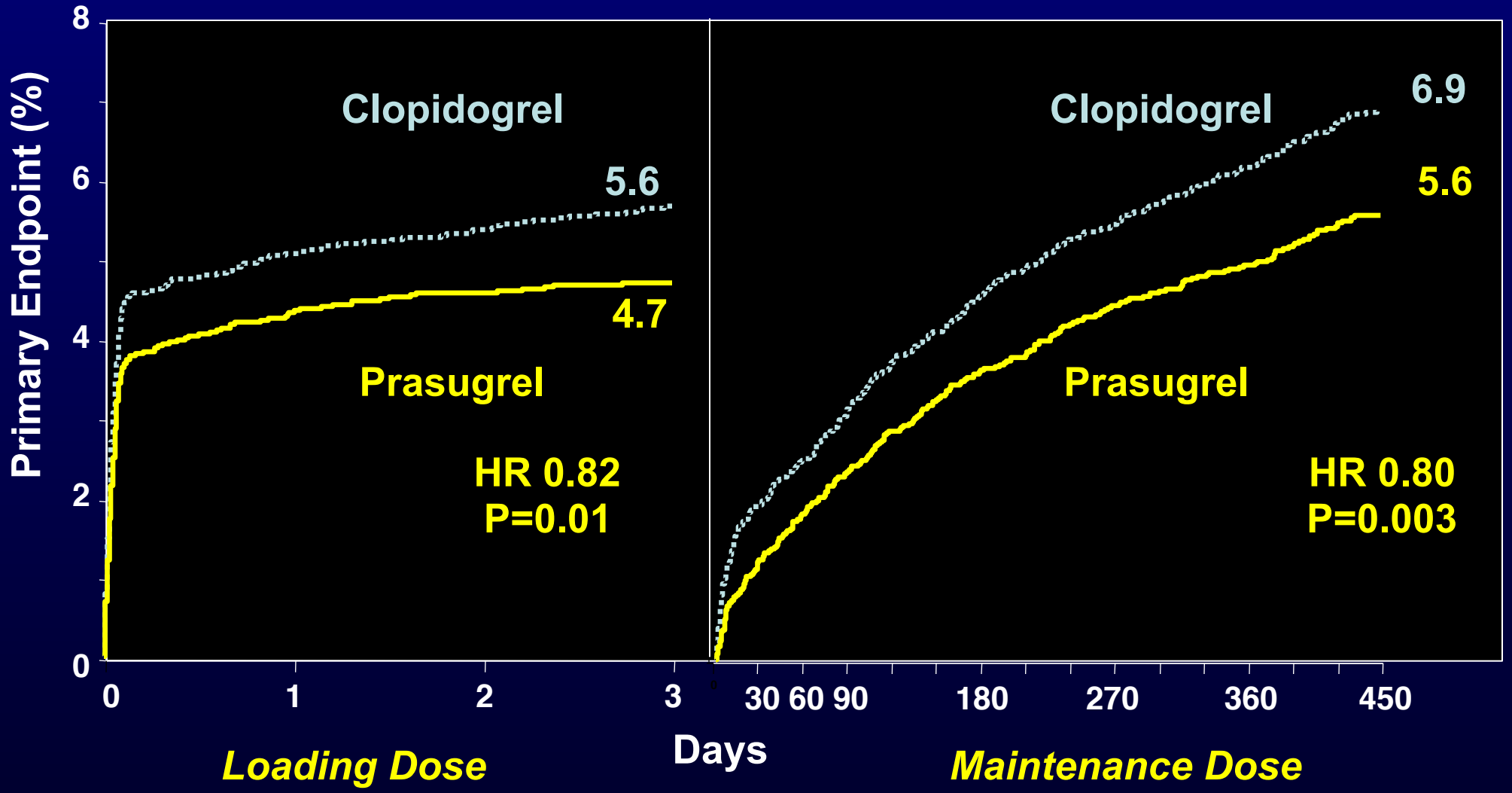
Timing of Benefit (Landmark Analysis)



Wiviott SD et al. NEJM 2007

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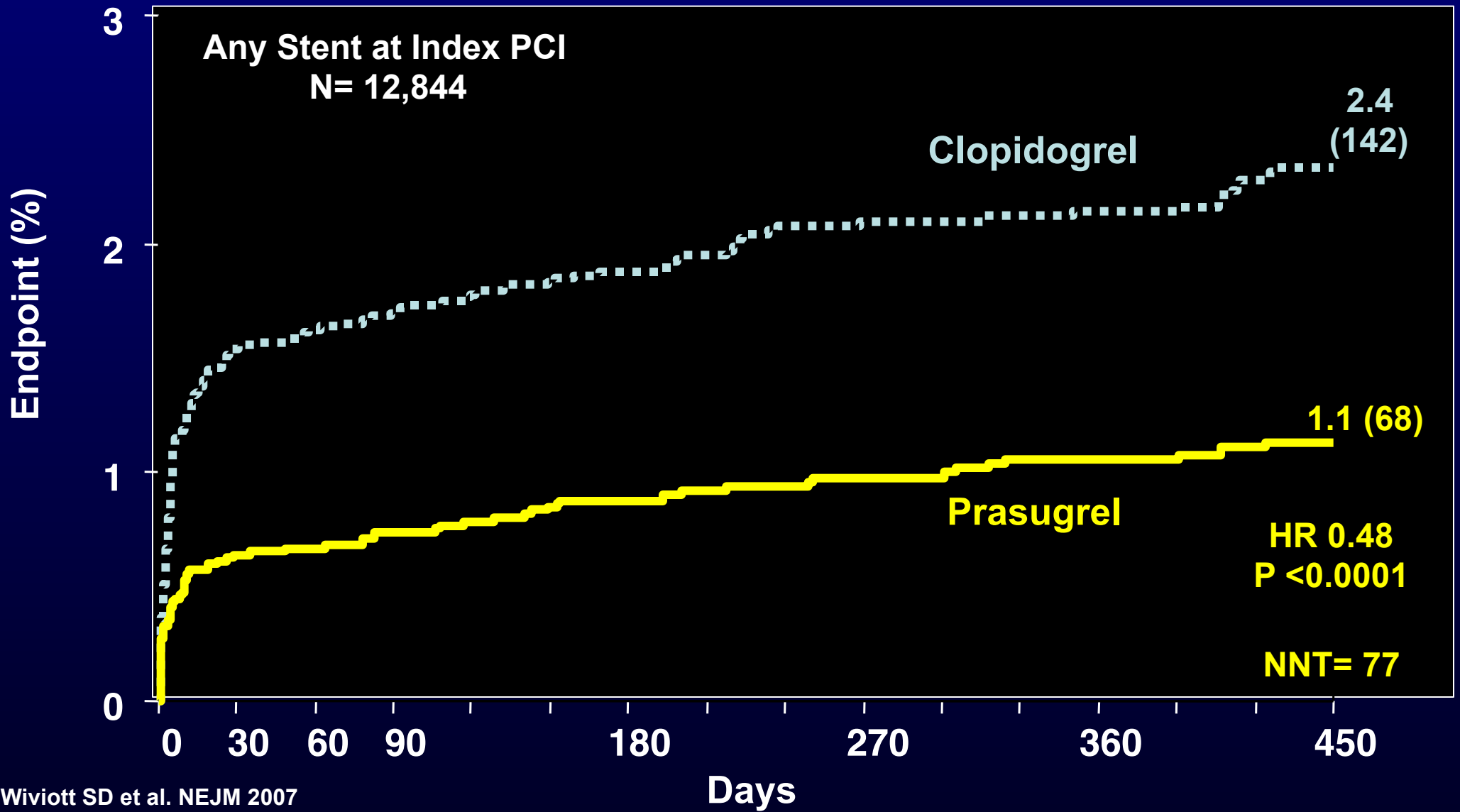
Stent Thrombosis (ARC Definite + Probable)



Wiviott SD et al. NEJM 2007

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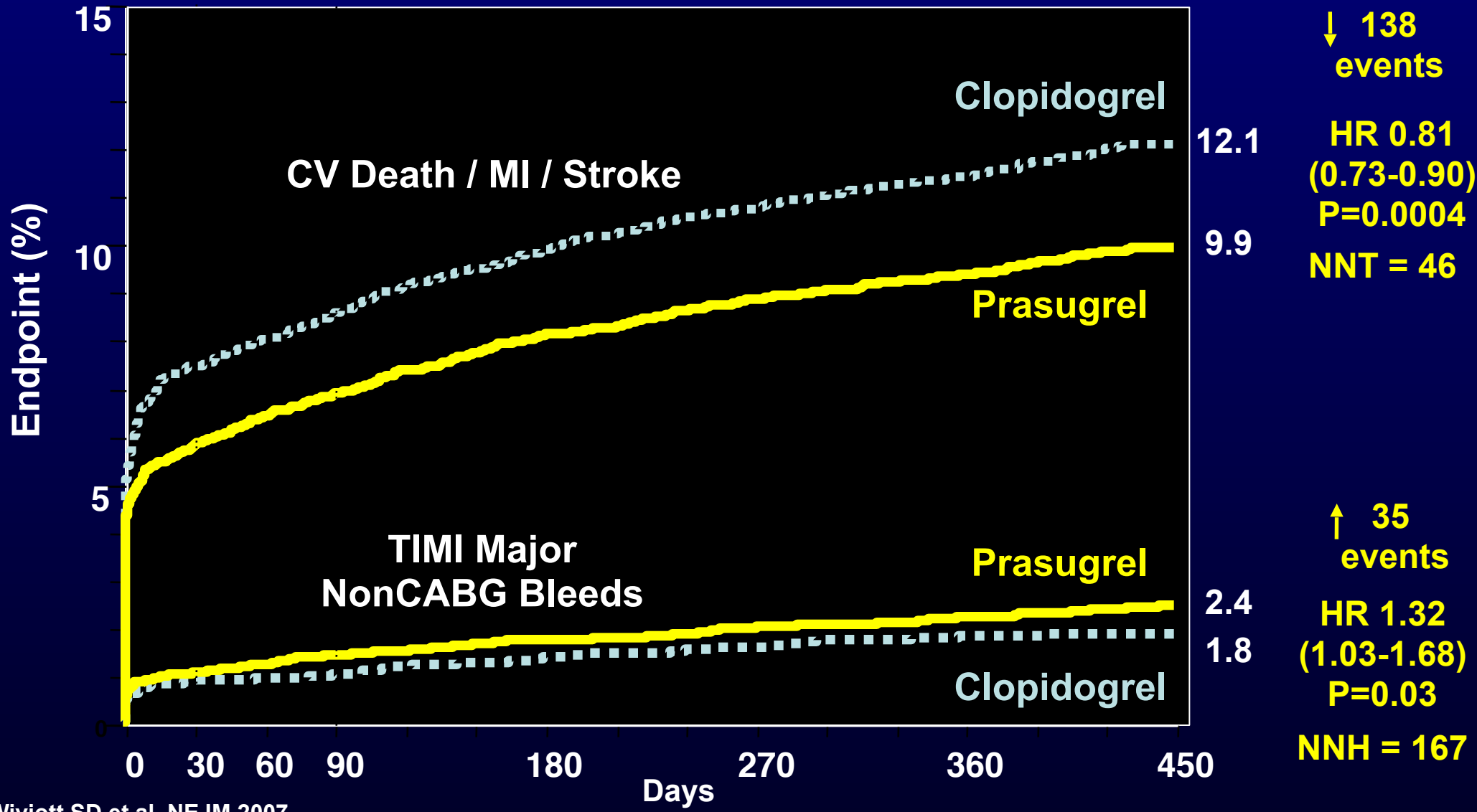
Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

↑ 35 events

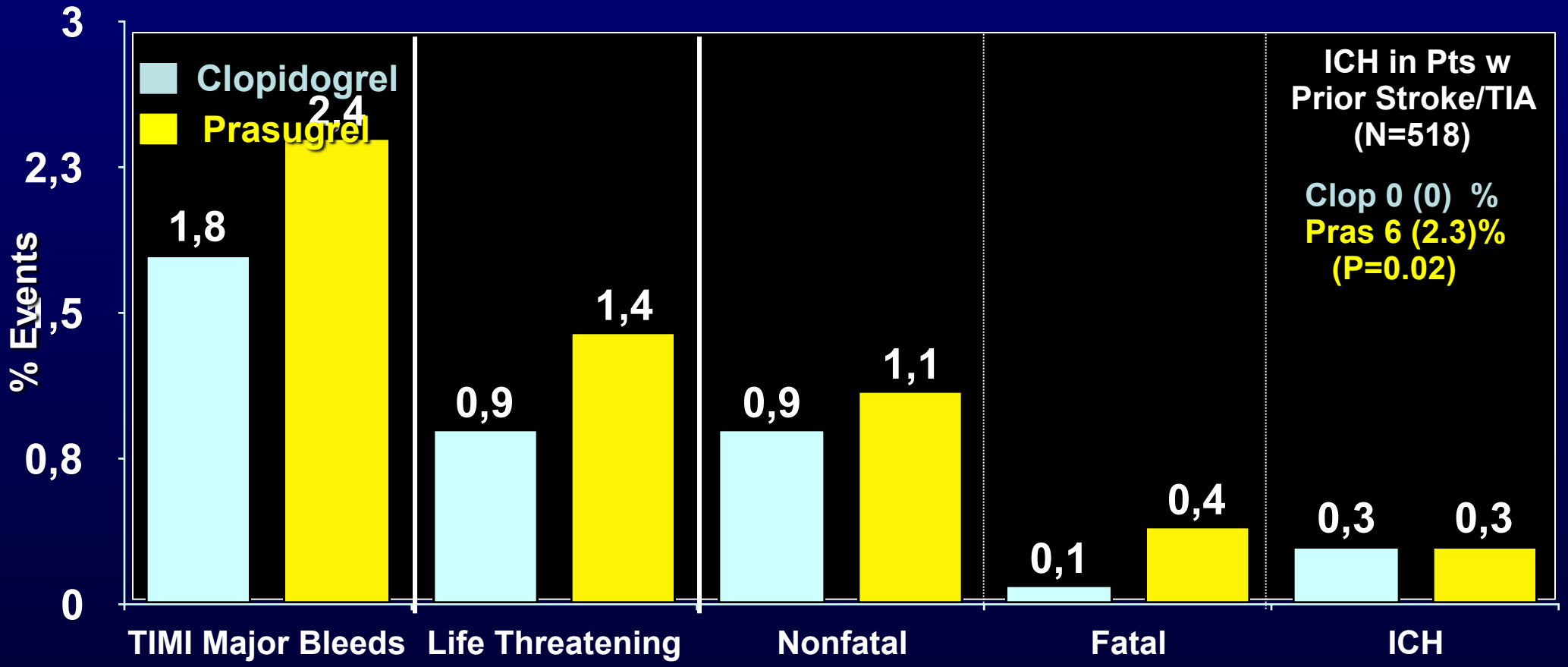
HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

Wiviott SD et al. NEJM 2007

TRÎTON TIMI·38

Bleeding Events
Safety Cohort
(N=13,457)



ARD 0.6%
HR 1.32
P=0.03
NNH=167

ARD 0.5%
HR 1.52
P=0.01

ARD 0.2%
P=0.23

ARD 0.3%
P=0.002

ARD 0%
P=0.74

Wiviott SD et al. NEJM 2007

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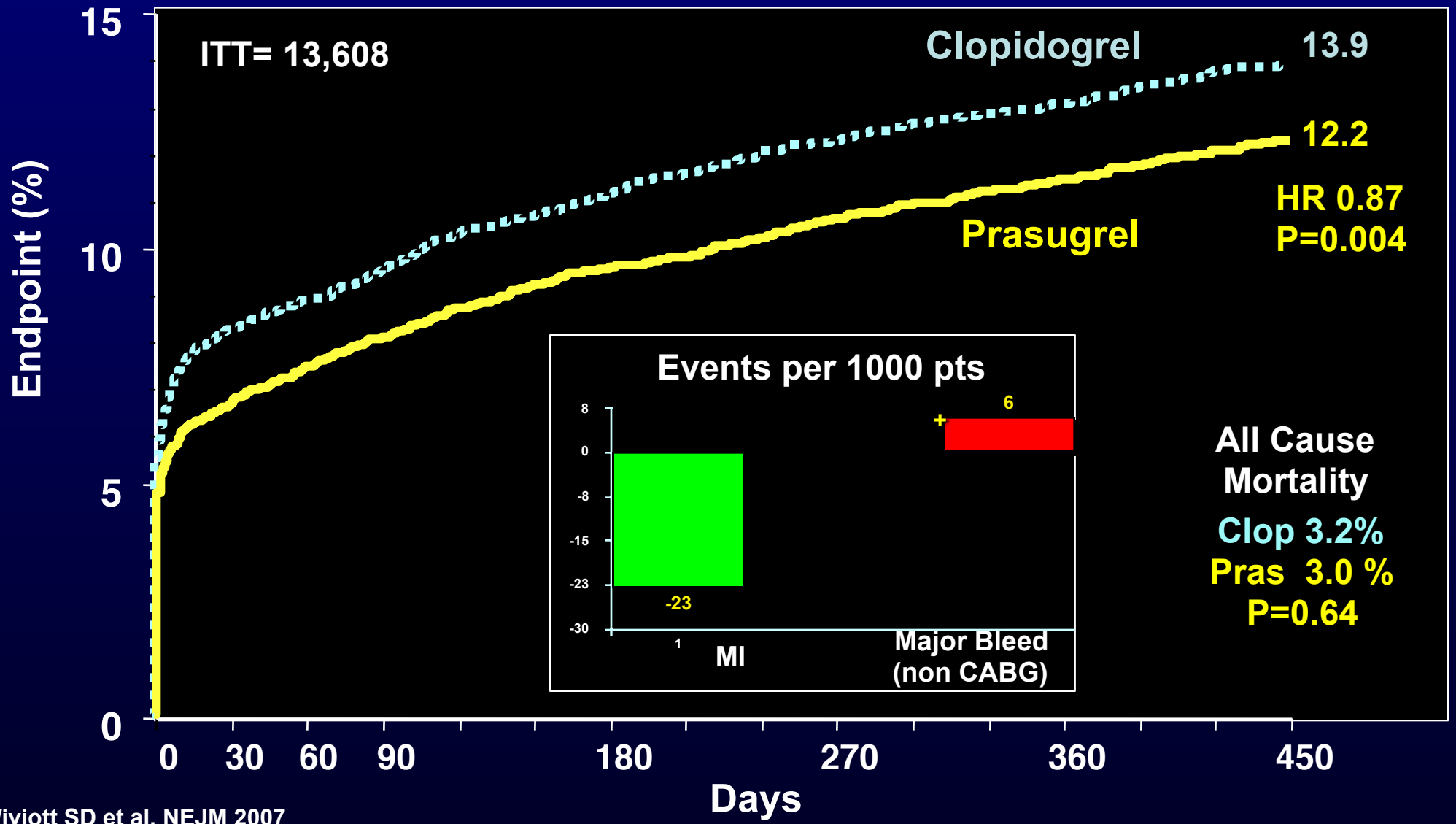
Net Clinical Benefit

Death, MI, Stroke, Major Bleed (non CABG)



Wiviott SD et al. NEJM 2007

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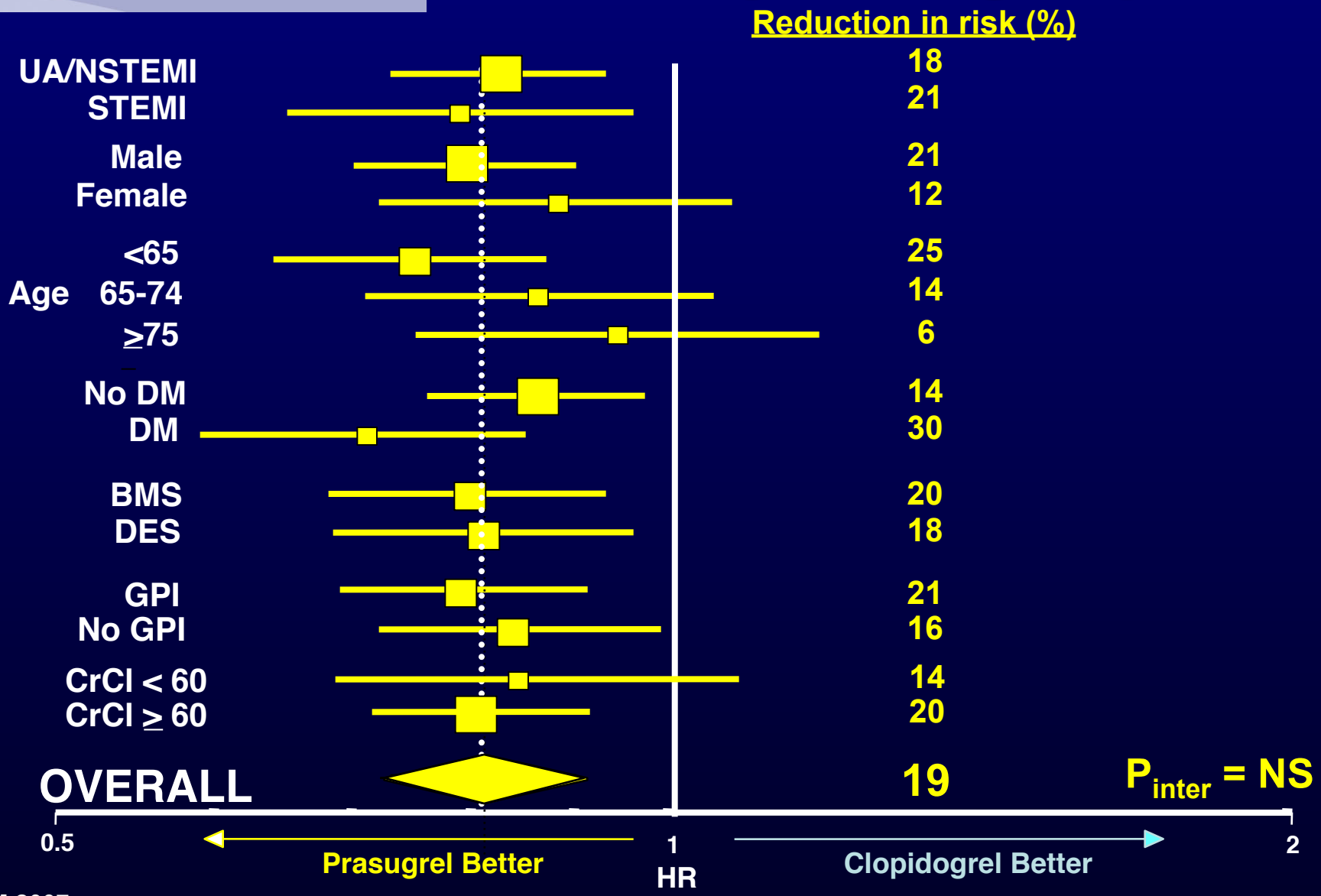
CV Death, MI, Stroke
Major Subgroups



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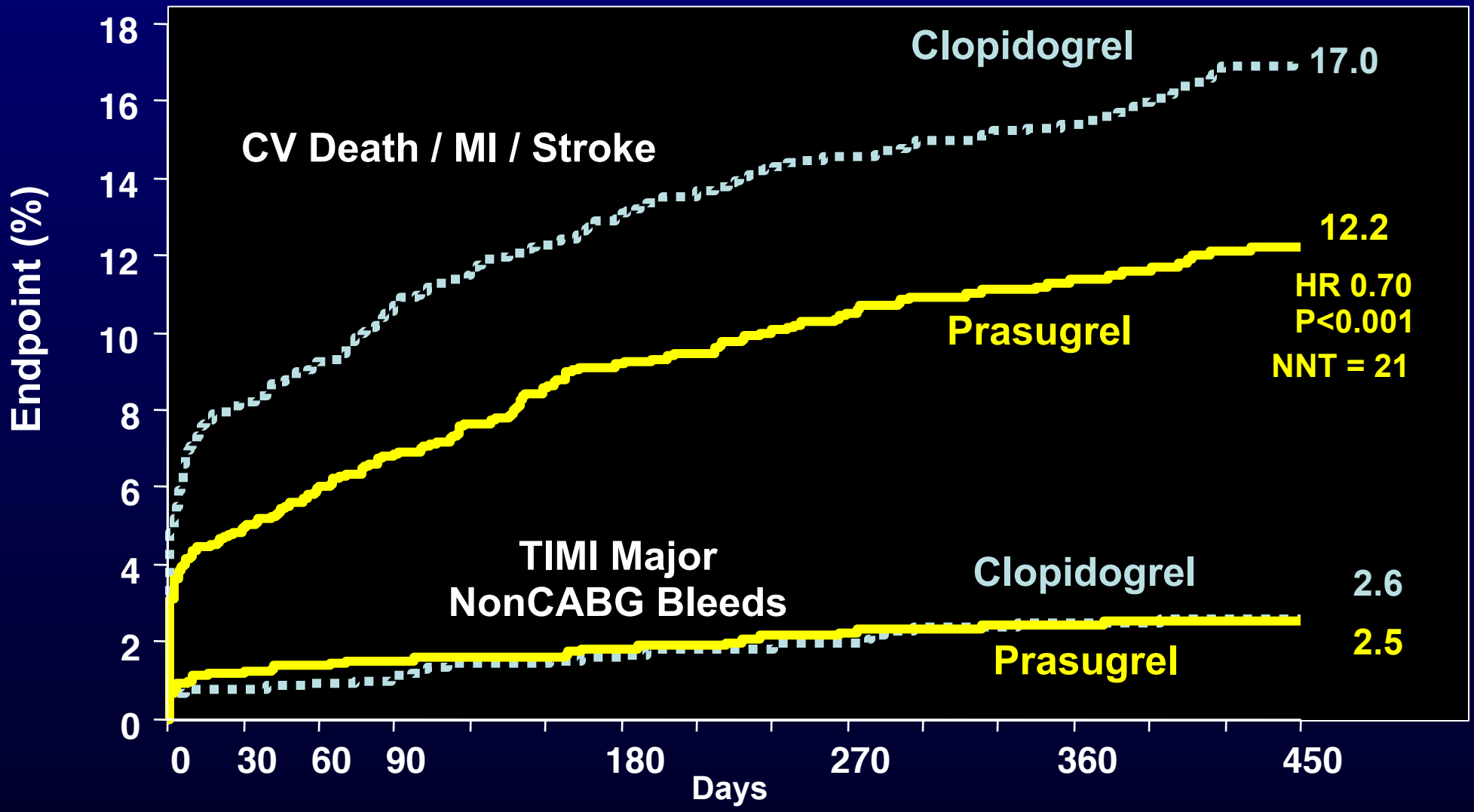
Diabetic Subgroup

N=3146



Wiviott SD et al. NEJM 2007

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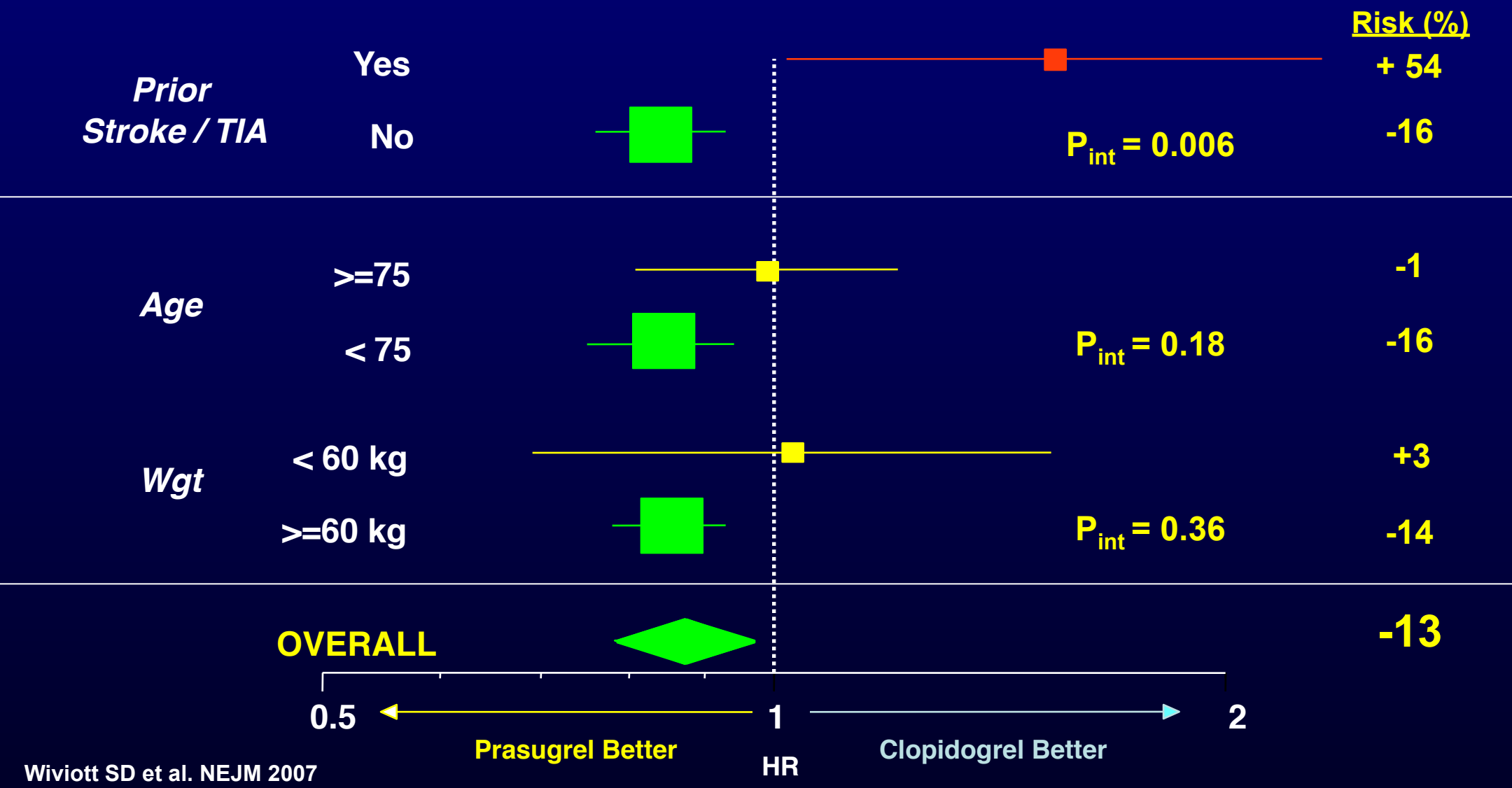
Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis



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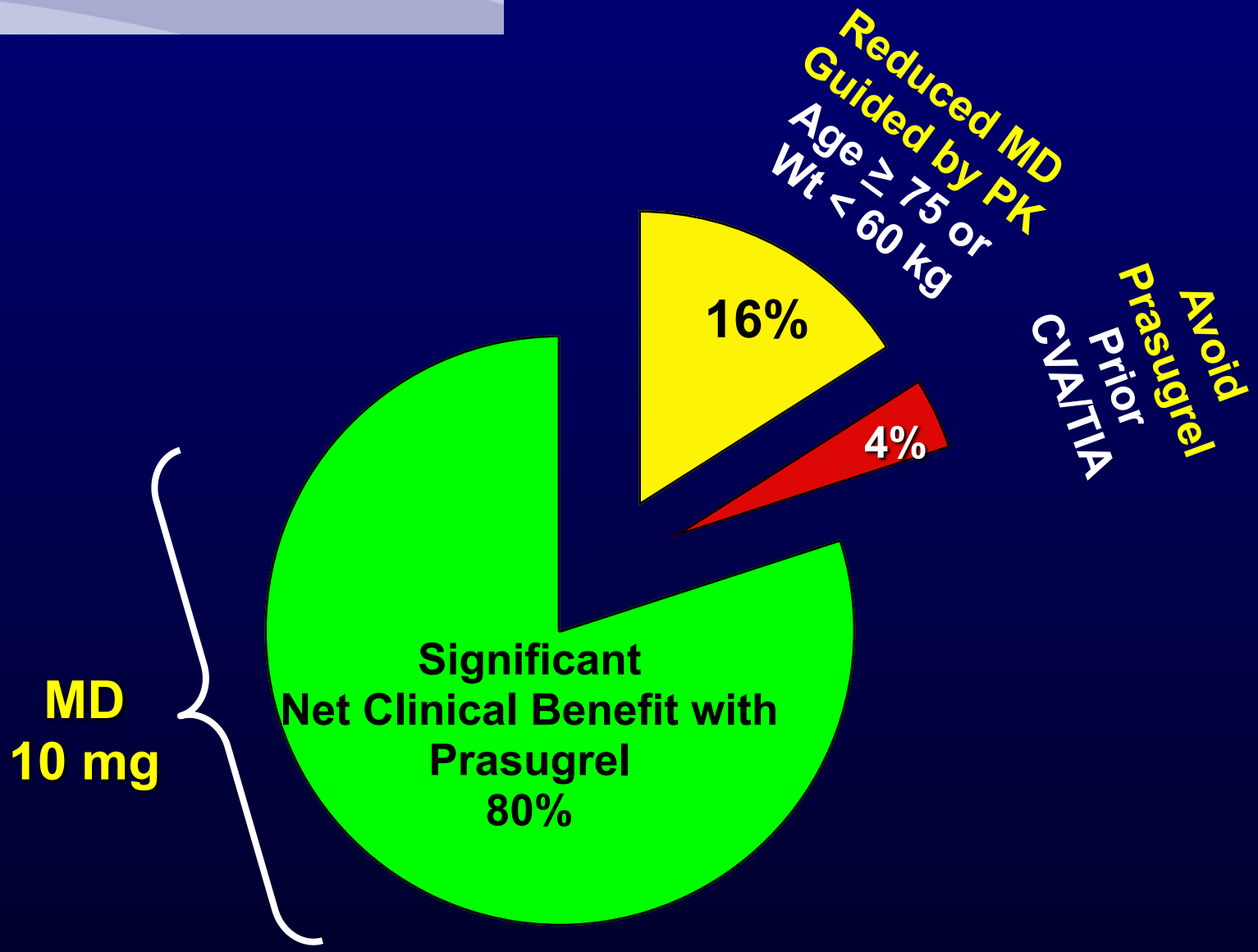
Bleeding Risk Subgroups
Therapeutic Considerations



Wiviott SD et al. NEJM 2007

TRÎTON TIMI·38

Conclusions

Higher IPA to Support PCI

Prasugrel 60 mg LD/10mg MD vs Clopidogrel 300 mg LD/ 75 mg MD

Efficacy

1. A significant reduction in:
   - *CV Death/MI/Stroke* 19%
   - Stent Thrombosis 52%
   - uTVR 34%
   - MI 24%
2. An early and sustained benefit
3. Across ACS spectrum

Safety

Significant increase in serious bleeding (32% increase)

Avoid in pts with prior CVA/TIA

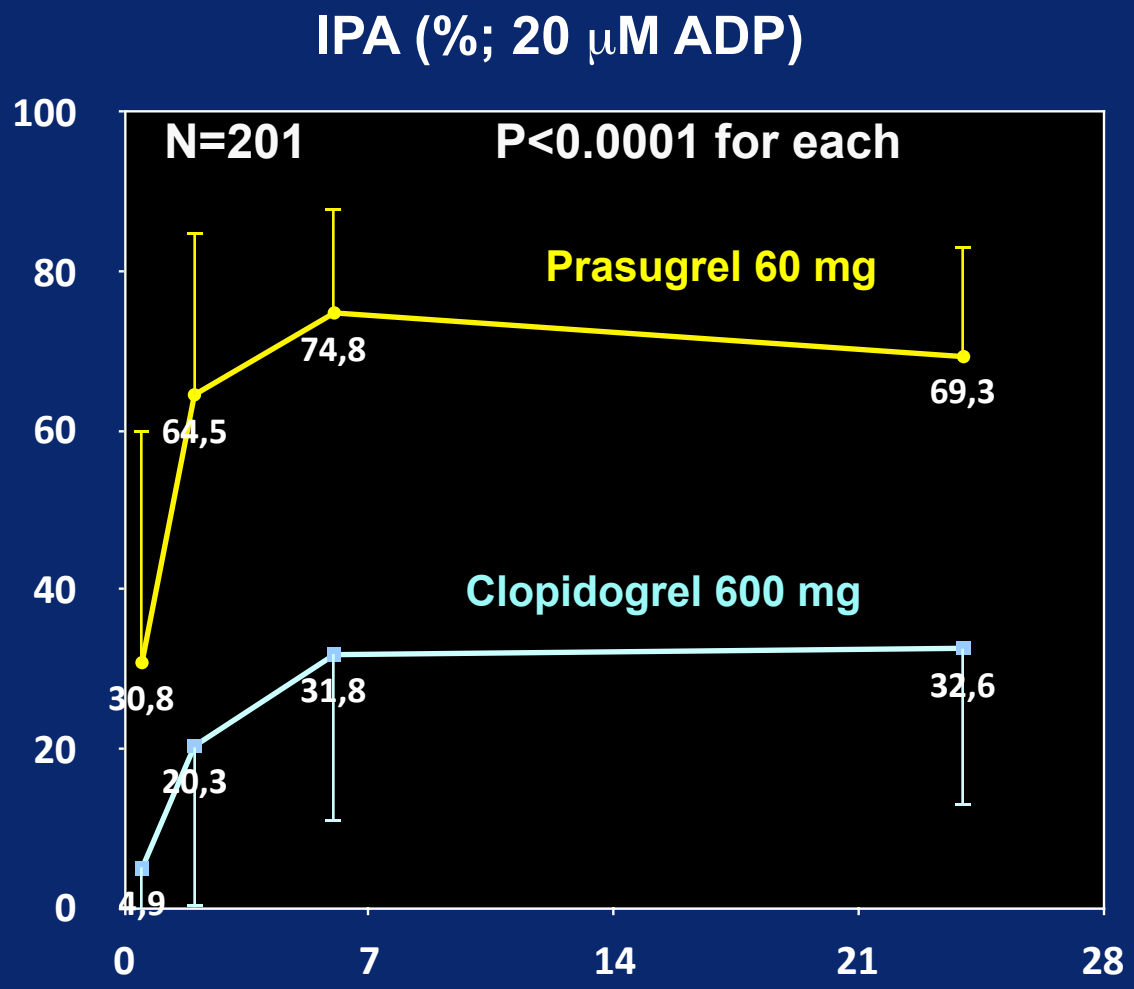
Net clinical benefit significantly favored Prasugrel

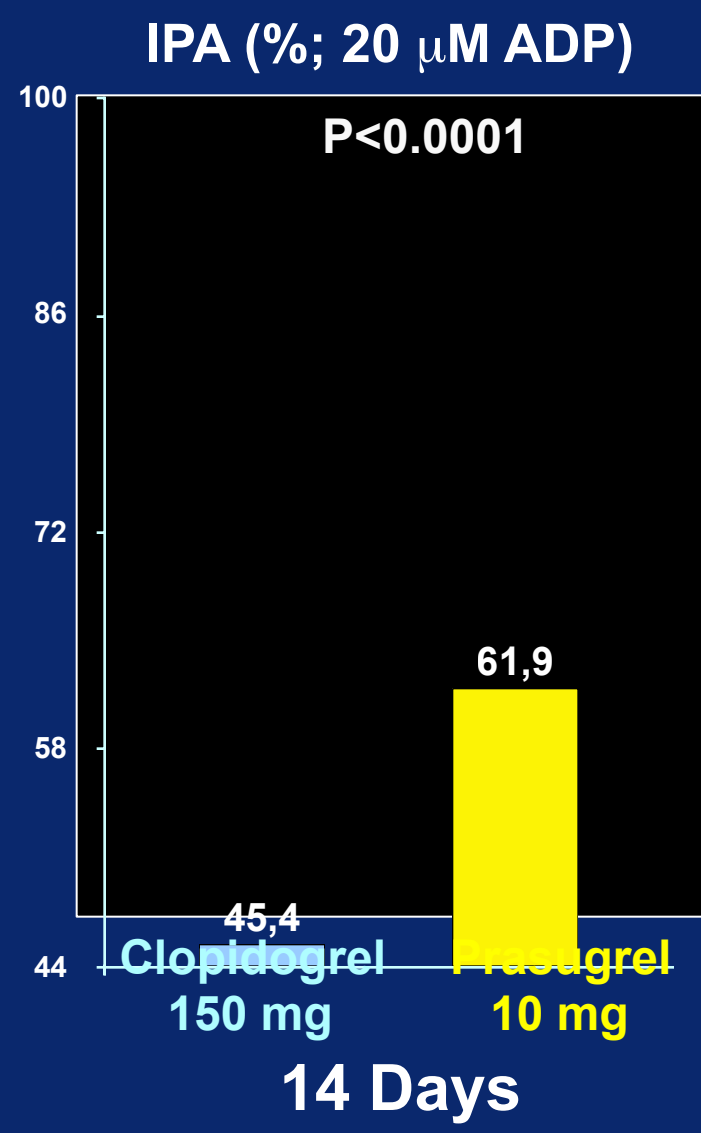
Optimization of Prasugrel maintenance dosing in a minority of patients may help improve the benefit : risk balance

Wiviott SD et al. NEJM 2007

PRINCIPLE TIMI 44

Comparison with Higher Dose Clopidogrel





Wiviott et al Circ 2007 (In Press)

Prasugrel studies in the pipeline

- **S.W.A.P.** – Phase II: Switching antiplatelet therapy (clopidogrel to prasugre)

- **ACAPULCO** – Phase II: Prasugrel vs high dose clopidogrel in ACS/PCI

- **TRILOGY** – Phase III:Prasugrel vs clopidogrel in non-revascularized ACS

Novel ADP $P2Y_{12}$ receptor antagonist

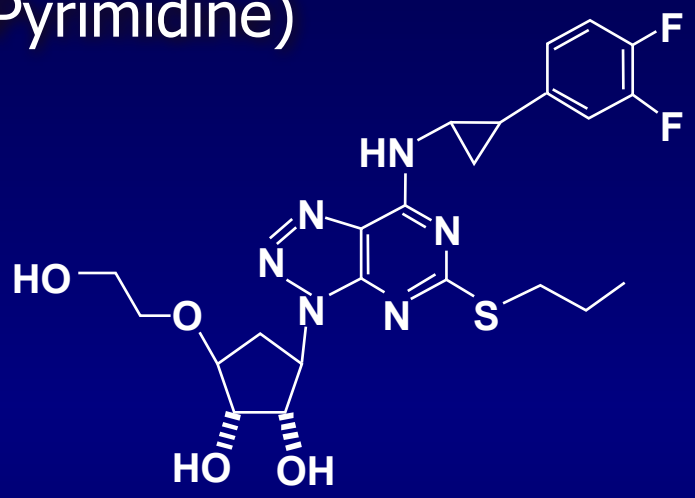
Prasugrel

AZD6140

Cangrelor

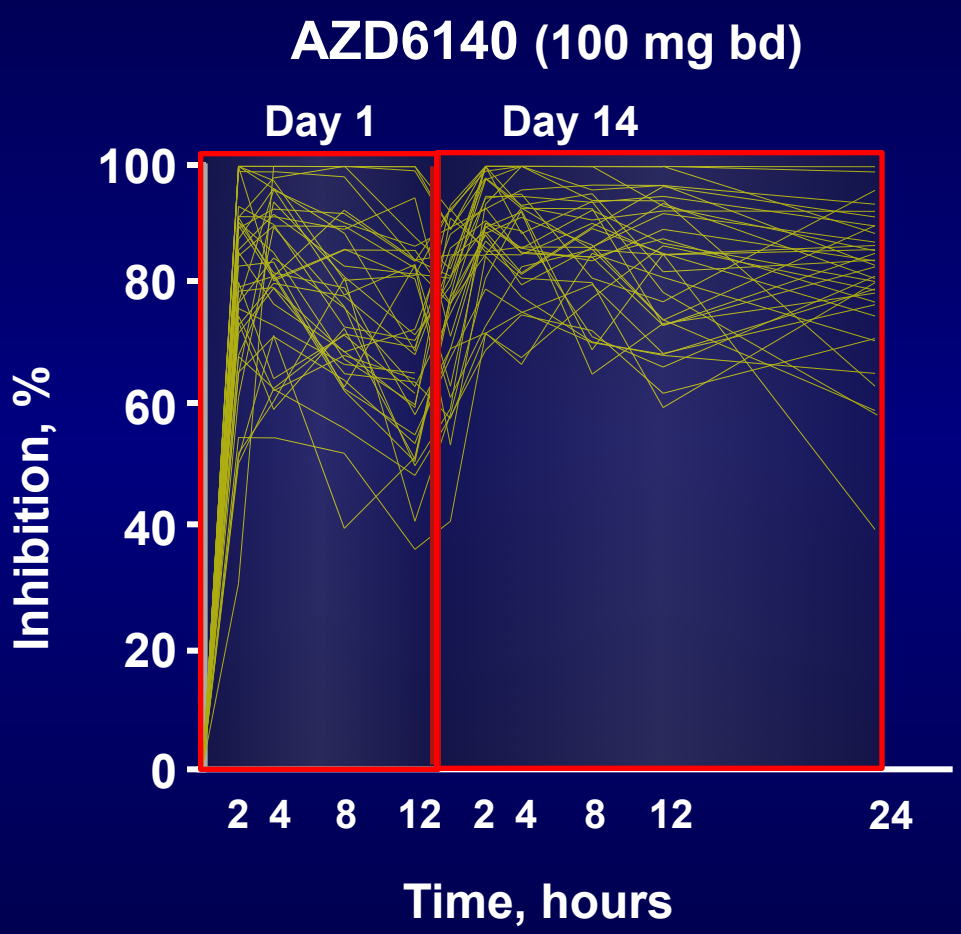
AZD6140

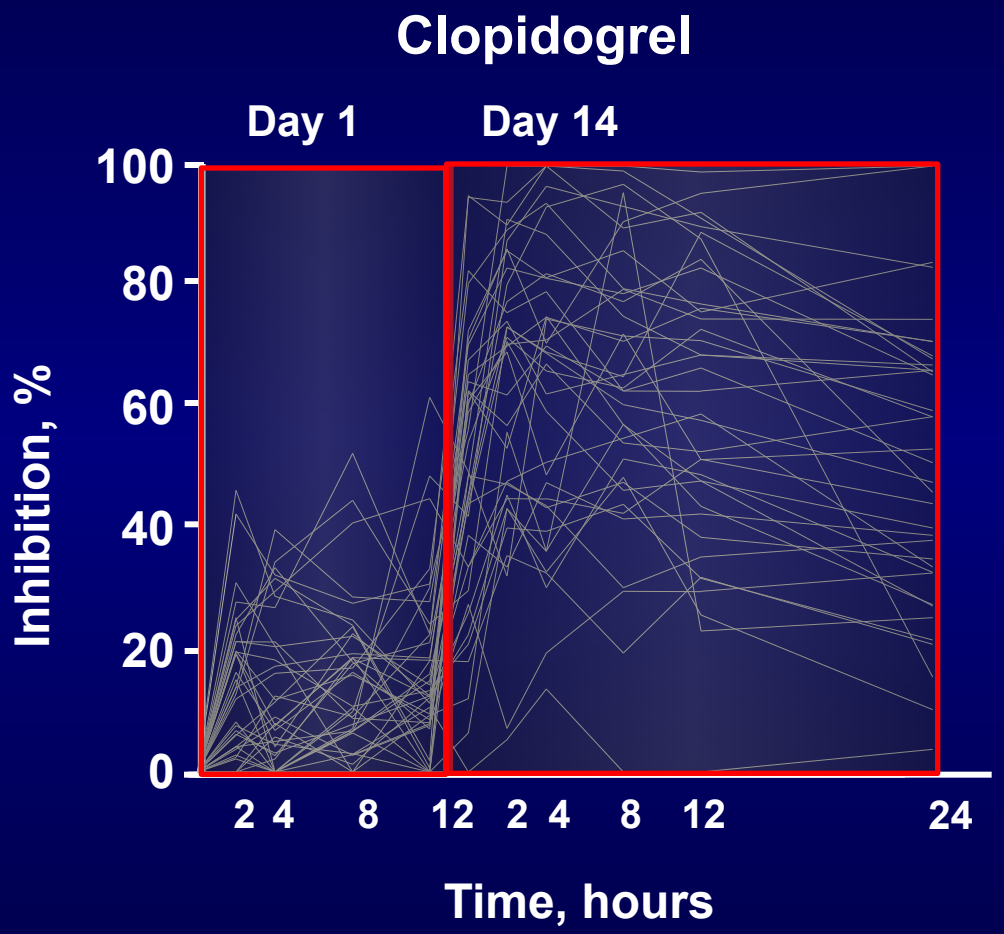
- A non-thienopyridine, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)



- First oral reversible ADP $P2Y_{12}$ receptor antagonist
- Direct acting via the $P2Y_{12}$ receptor - metabolism not required for activity
- More potent platelet inhibitor than clopidogrel

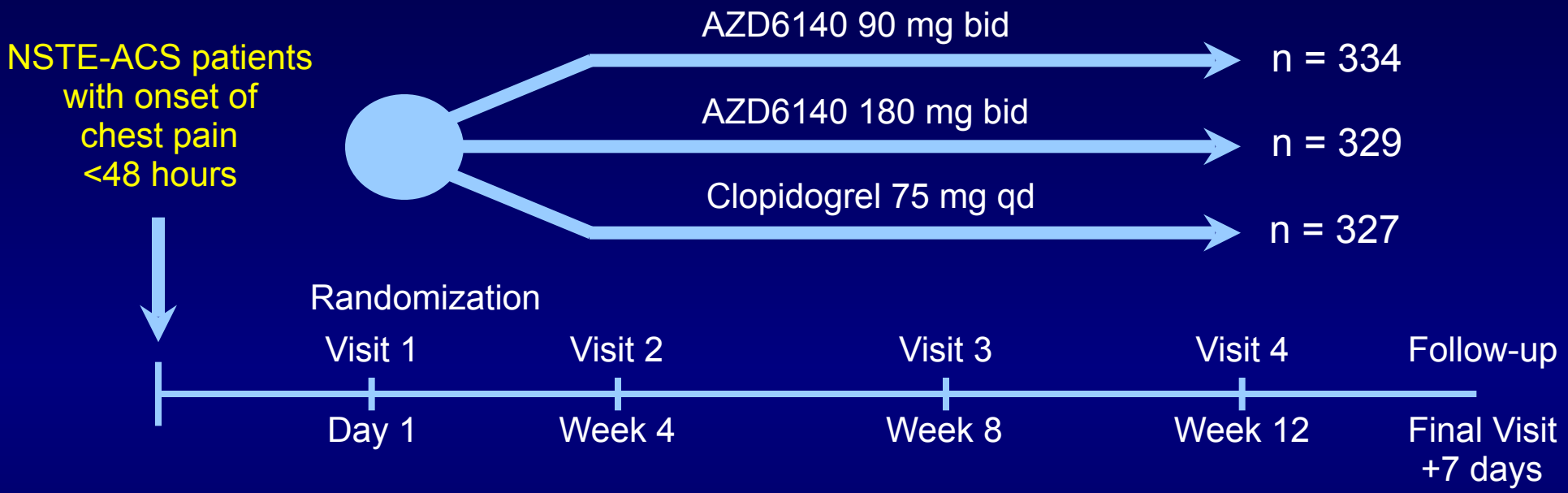
DISPERSE: Faster, Greater and More Consistent IPA with AZD6140 vs clopidogrel





Husted SE et al Eur Heart J 2006; 27: 1038-1047

DISPERSE2 Study Design

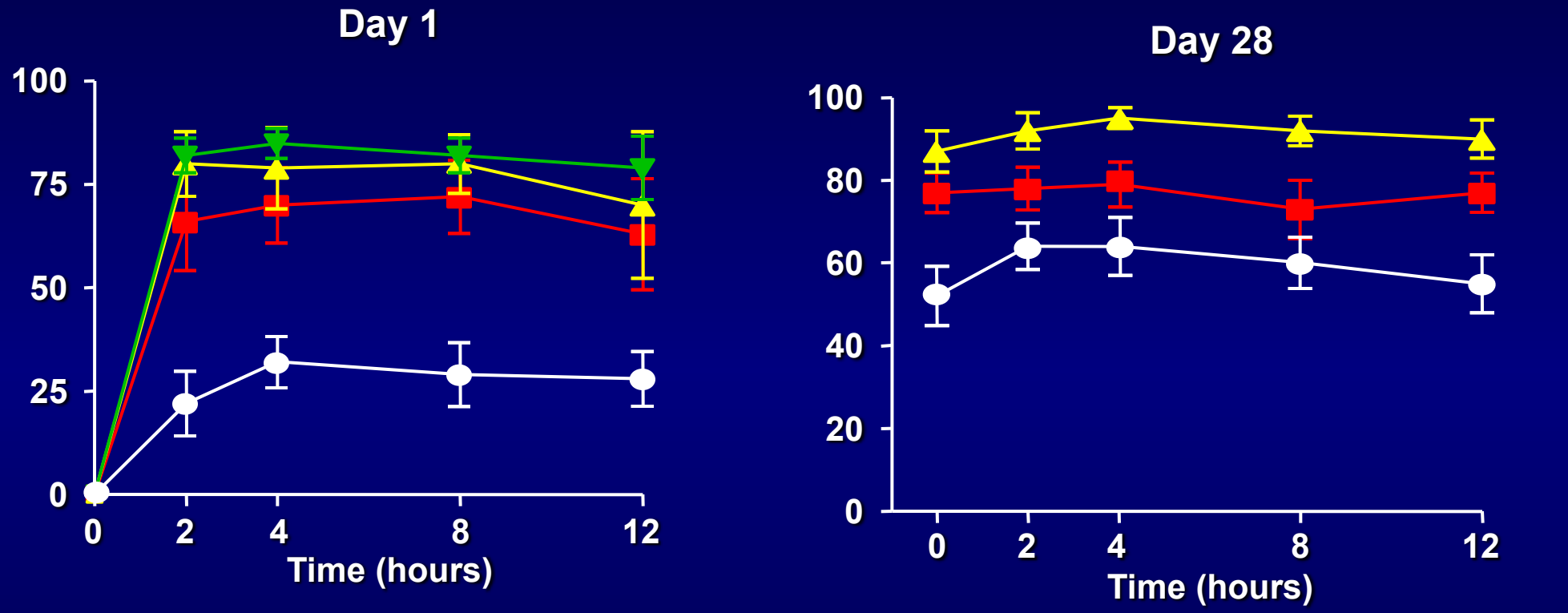


- DISPERSE2 was a double-blind, randomized study of AZD6140 compared with clopidogrel, both on a background of aspirin (75–100 mg od)
- 50% of patients in each AZD6140 arm received a loading dose of 270 mg
- In the clopidogrel arm, thienopyridine treatment-naïve patients received a 300-mg loading dose

Cannon CP et al. *J Am Coll Cardiol* 2007;50:1844-51

DISPERSE-2: Final Inhibition of Platelet Aggregation (IPA)

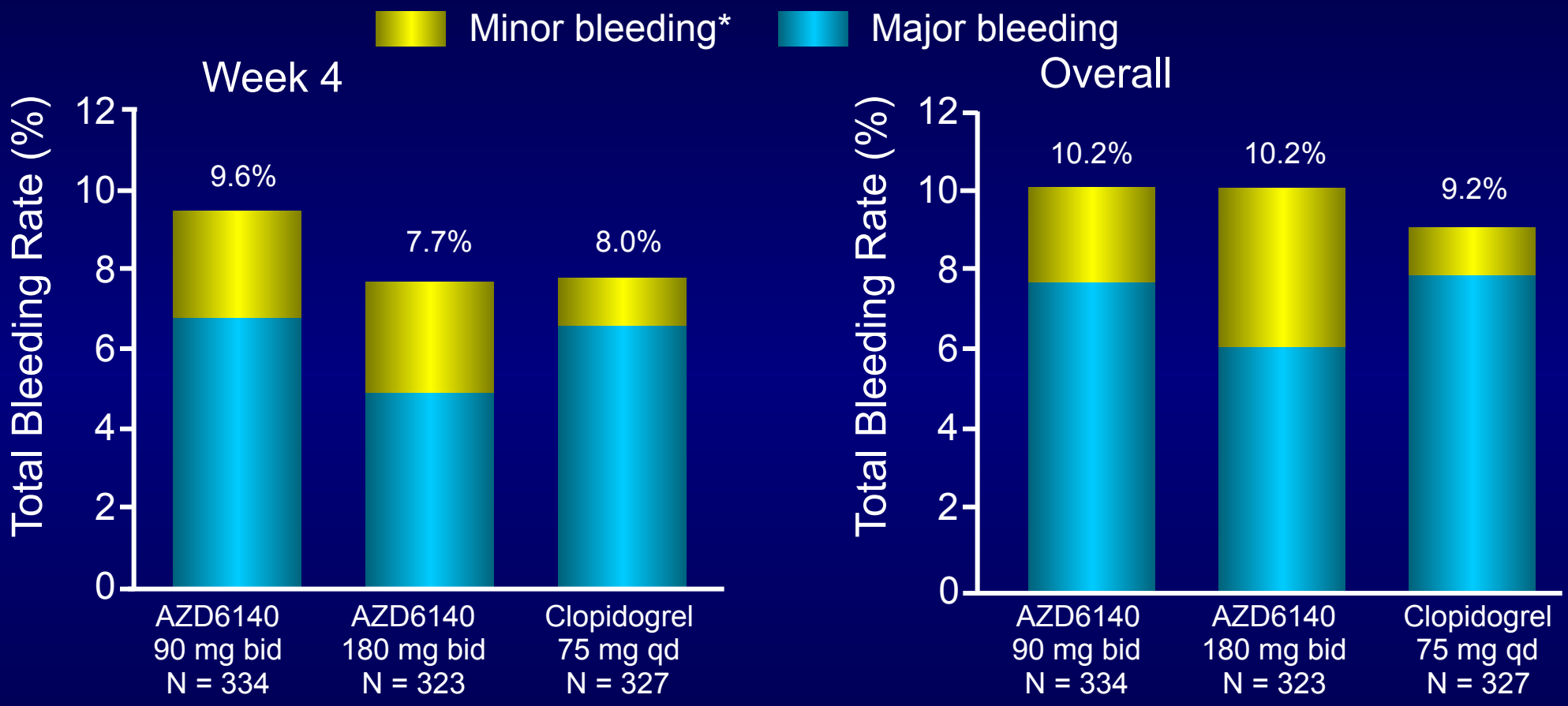
(Clopidogrel-Naïve Patients)



***P*<0.05 for both AZD6140 groups vs clopidogrel at 4 h on day 1 *and* for 180 mg on day 28 and for 90 mg at 0 and 12 h on day 28**

R Storey et al. *J Am Coll Cardiol*. 2007;50:1852-6.

DISPERSE2 Adjudicated Bleeding Rates (%) Week 4 and Overall



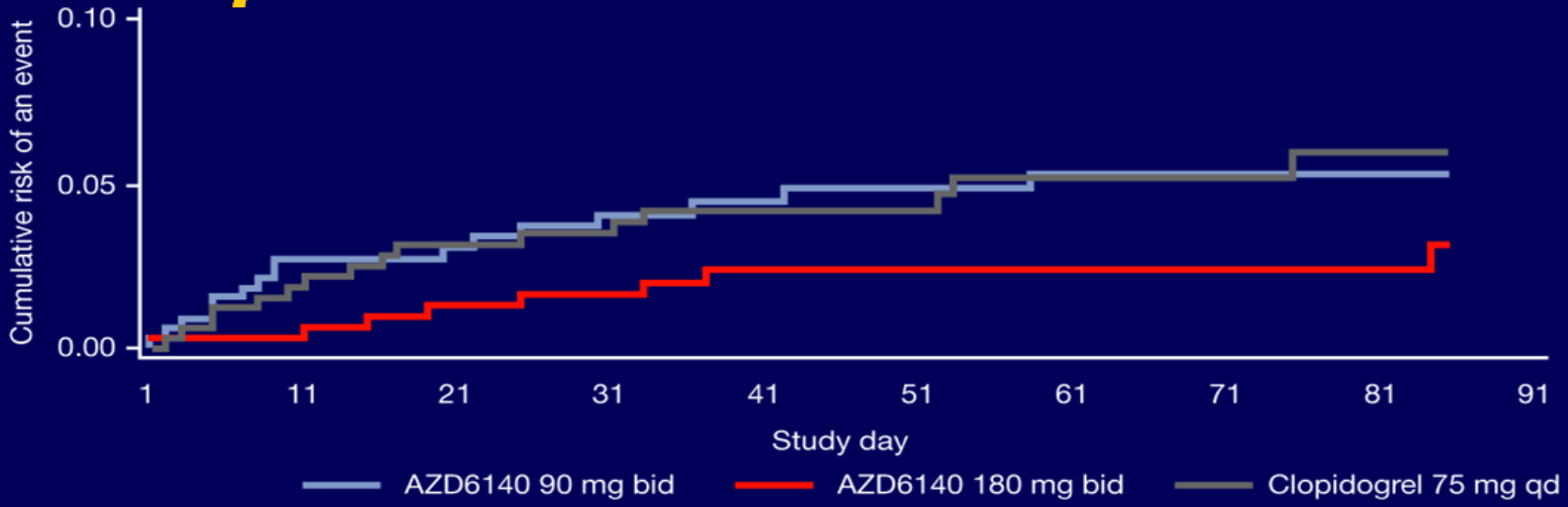
- Adjudicated total bleeding rates were similar for all groups
- No evidence of dose-response for major bleeds

* Minor bleeding without major bleeding

Cannon CP et al. *J Am Coll Cardiol* 2007;50:1844-51

DISPERSE2

Cumulative adjudicated clinical end point of CV death/MI/stroke



- **No significant differences found between the groups for clinical end points**

Cannon CP et al. *J Am Coll Cardiol* 2007;50:1844-51

DISPERSE2

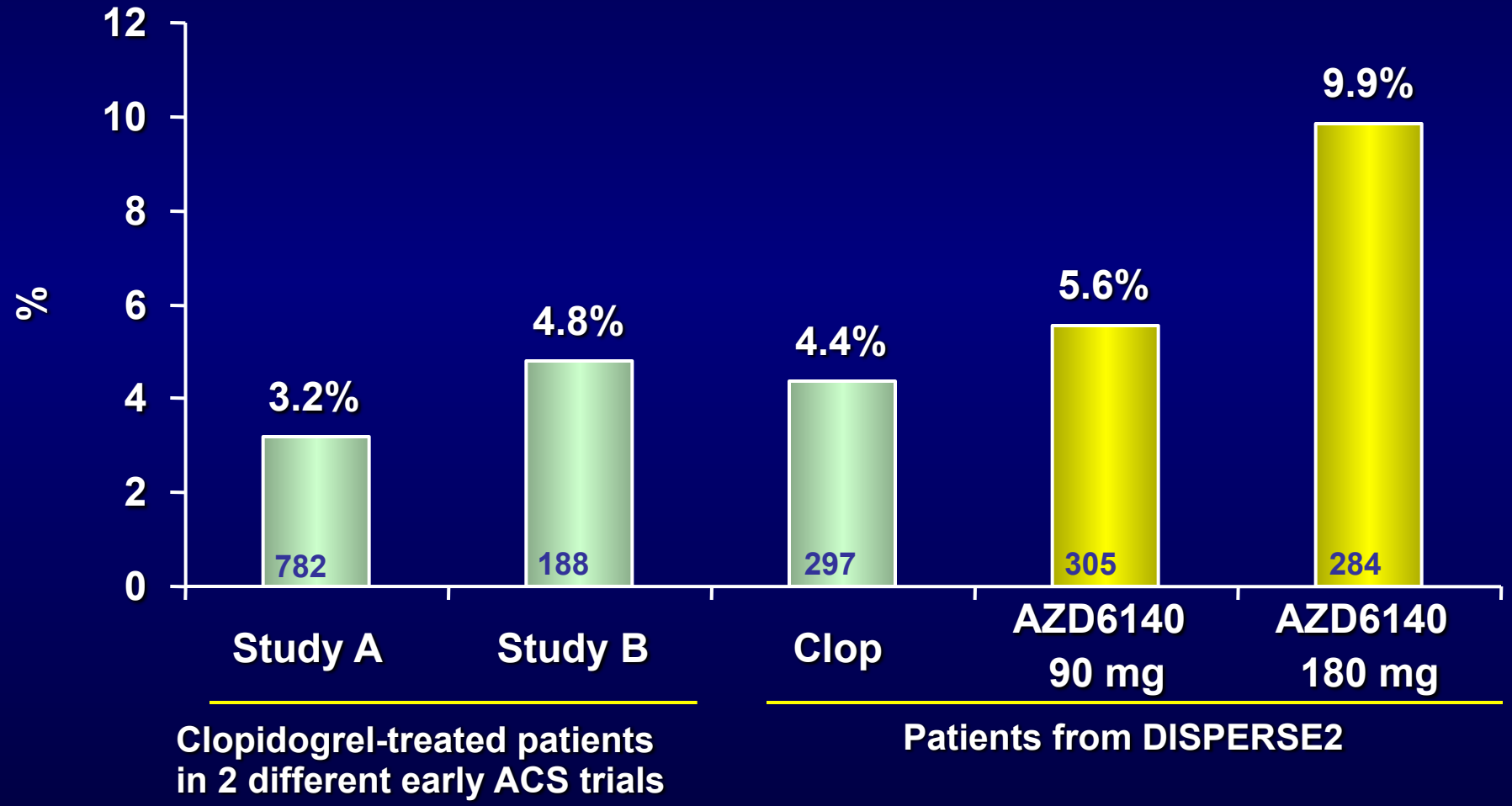
Non-bleeding adverse events (%)

Preferred term	AZD6140 90 mg bid n=334	AZD6140 180 mg bid n=323	Clopidogrel 75 mg qd n=327
Dyspnea	10.5	15.8	6.4
Chest pain	7.5	7.4	8.9
Headache	9.6	6.5	8.6
Nausea	6.6	6.5	3.4
Dyspepsia	4.8	3.1	2.8
Insomnia	5.4	4.6	2.8
Diarrhea	3.0	7.4	3.4
Hypotension	4.2	3.7	0.6

- Discontinuation rates due to adverse events were low and similar between the groups
  - 21 (6%), 23 (7%) and 19 (6%) discontinued in the AZD6140 90 mg bid, AZD6140 180 mg bid and clopidogrel 75 mg qd groups, respectively

Cannon CP et al. *J Am Coll Cardiol* 2007;50:1844-51

Ventricular Pauses >2.5 Seconds in Context of Other Studies



Moderate- to high-risk ACS patients (UA/NSTEMI/STEMI, PCI, medically managed, or CABG)

(N=18,000)

ASA + Clopidogrel
300 mg ld/75 mg qd
600 mg ld allowed in PCI

ASA + AZD6140
180 mg ld/90 mg bid

12-month maximum exposure
(Min = 6 mo, Max = 12 mo, Mean = 11 mo)

Primary endpoint: CVD/MI/stroke

Secondary endpoint: CVD/MI/stroke/revascularization with PCI; CVD/MI/stroke, severe recurrent ischemia

ASA = acetylsalicylic acid; bid = twice daily; CVD = cardiovascular disease; ld = loading dose; MI = myocardial infarction; NSTEMI = non-ST-segment elevation MI; qd = once daily; STEMI = ST-segment elevation MI; UA = unstable angina.

ClinicalTrials.gov Identifier: NCT00391872

Novel ADP $P2Y_{12}$ receptor antagonist

Prasugrel

AZD6140

Cangrelor

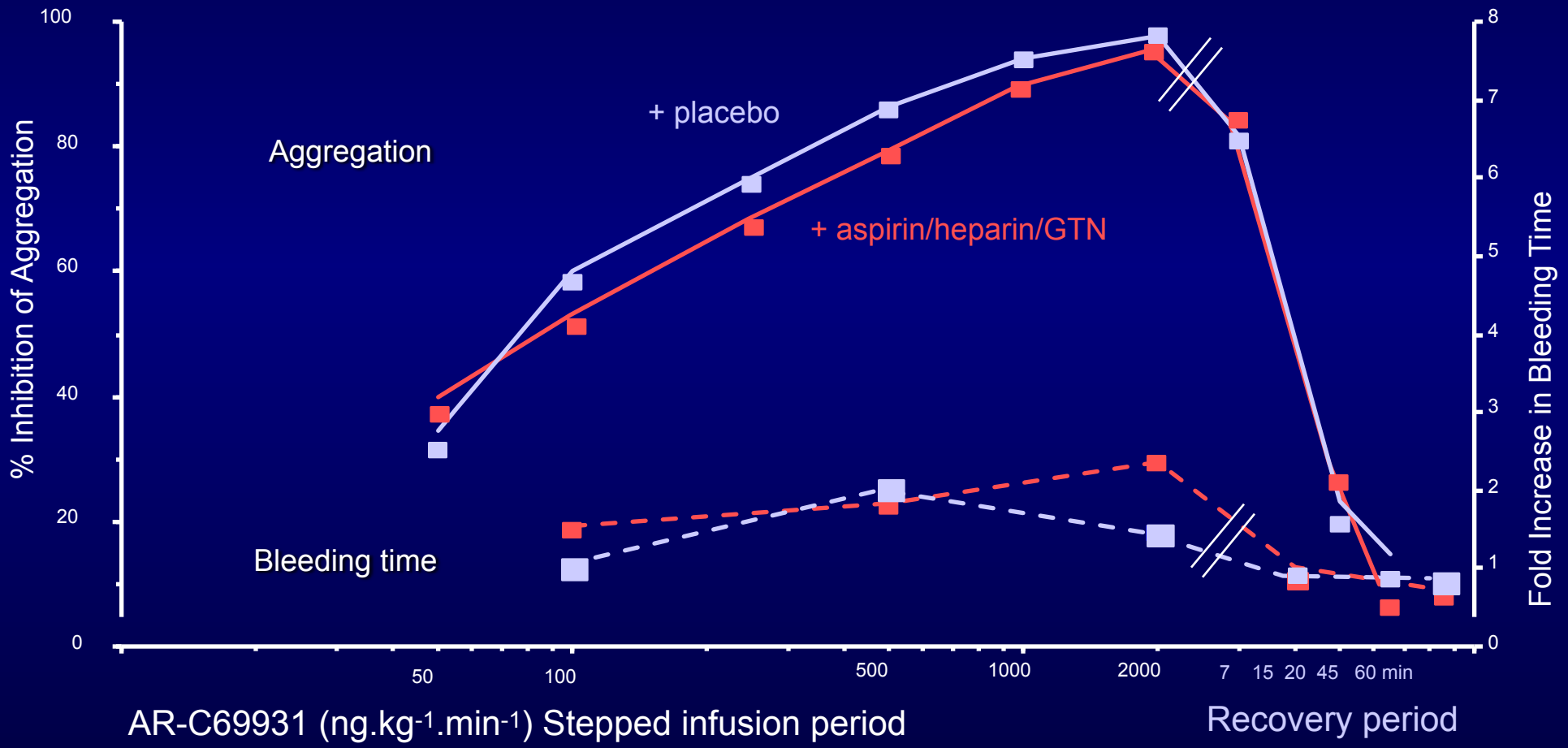
Cangrelor (AR-C69931MX)

- **Parenteral** ADP-$P2Y_{12}$ receptor antagonist
- ATP analogue

- **Direct** and **Reversible** $P2Y_{12}$ inhibitor
- **More potent** than clopidogrel ~90% inhibition of platelet aggregation at 1 - 4 mcg/kg/min iv
- Plasma half-life of 5-9 min.; 20 min. for return to normal platelet function

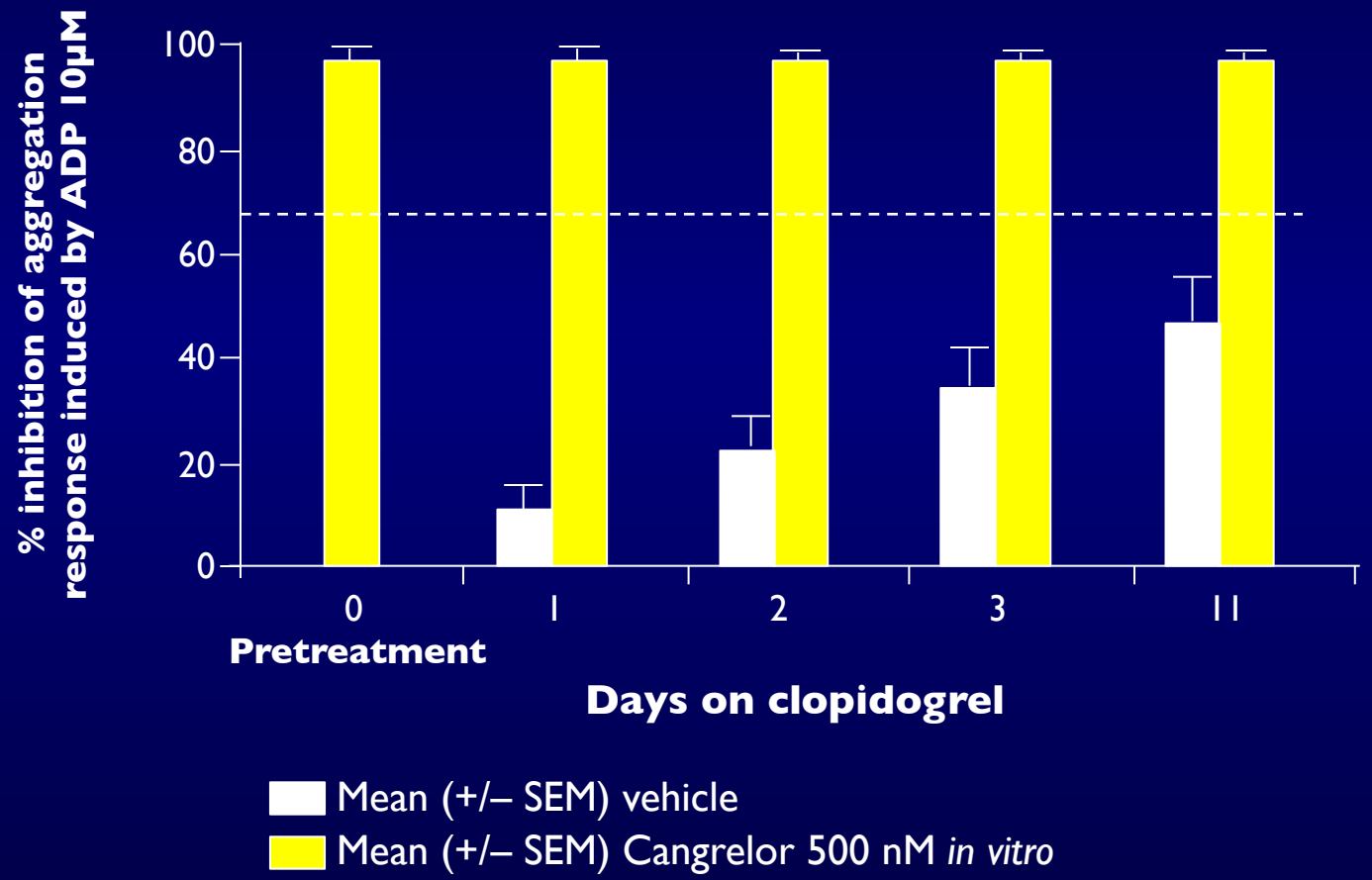
Key Phase I result

Rapid reversal of dose-dependent effect



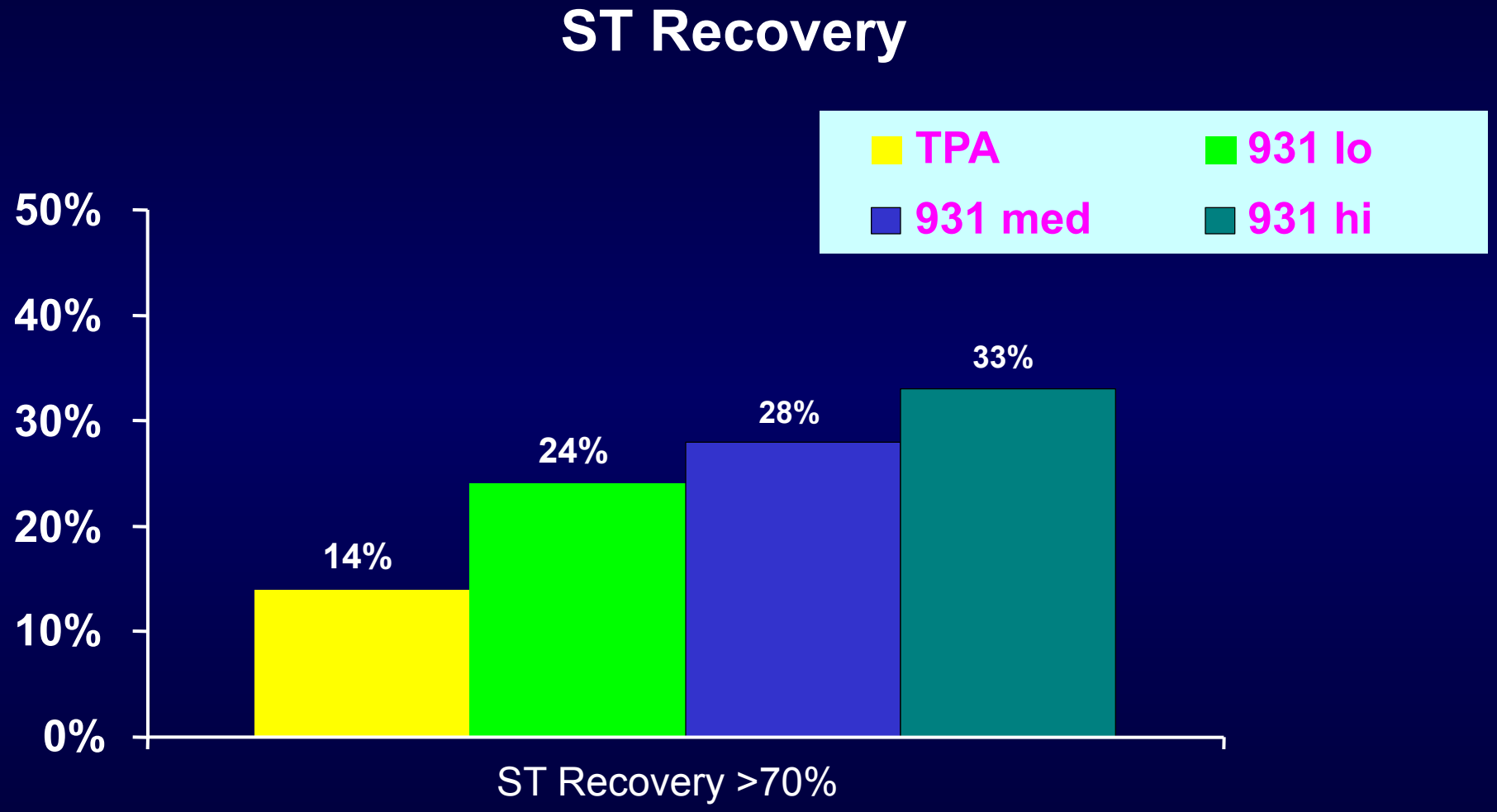
Cangrelor with Clopidogrel

Cangrelor improves platelet inhibition in patients receiving chronic clopidogrel



Storey RF, et al., *Thromb Haemost* 2002; 88: 488-94

Cangrelor + tPA in STEMI

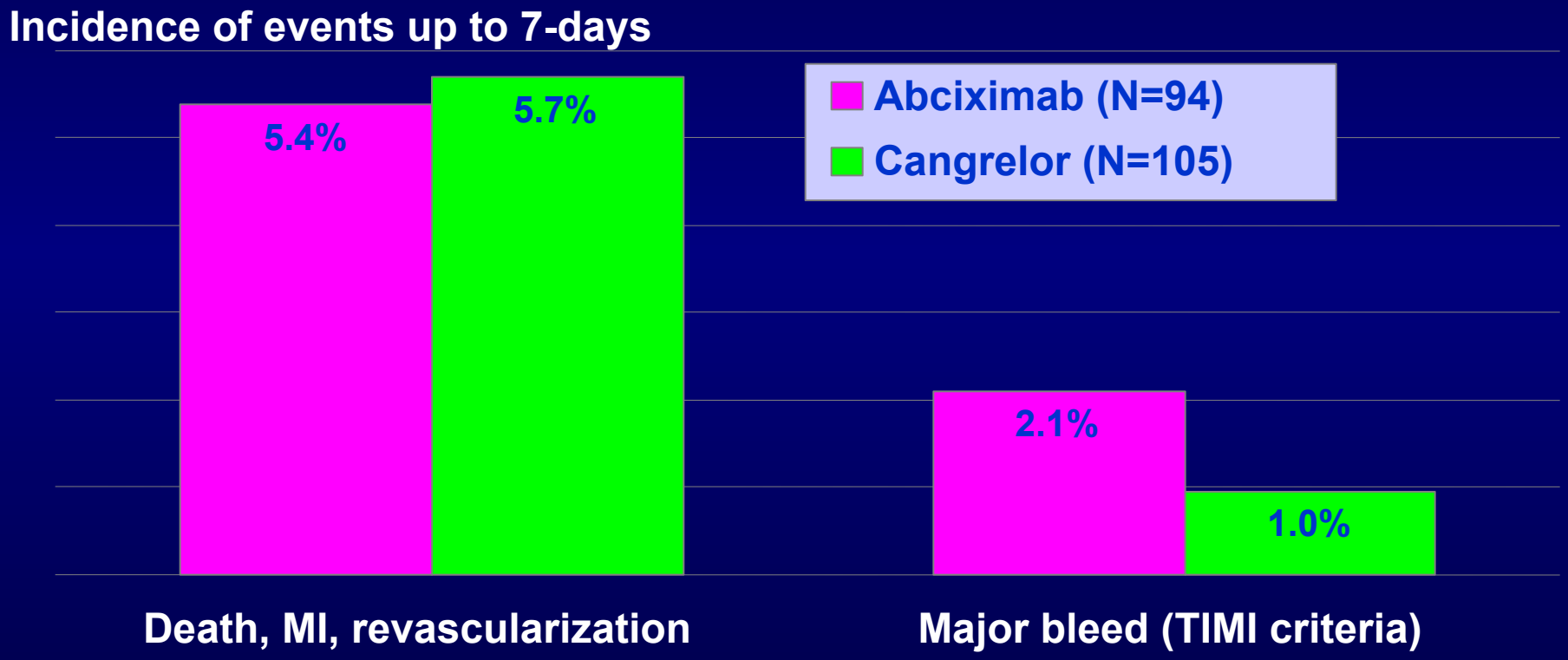


Greenbaum et al. ACC 2002.

SC-931-5135

Phase II clinical data: Compared with Abciximab in PCI

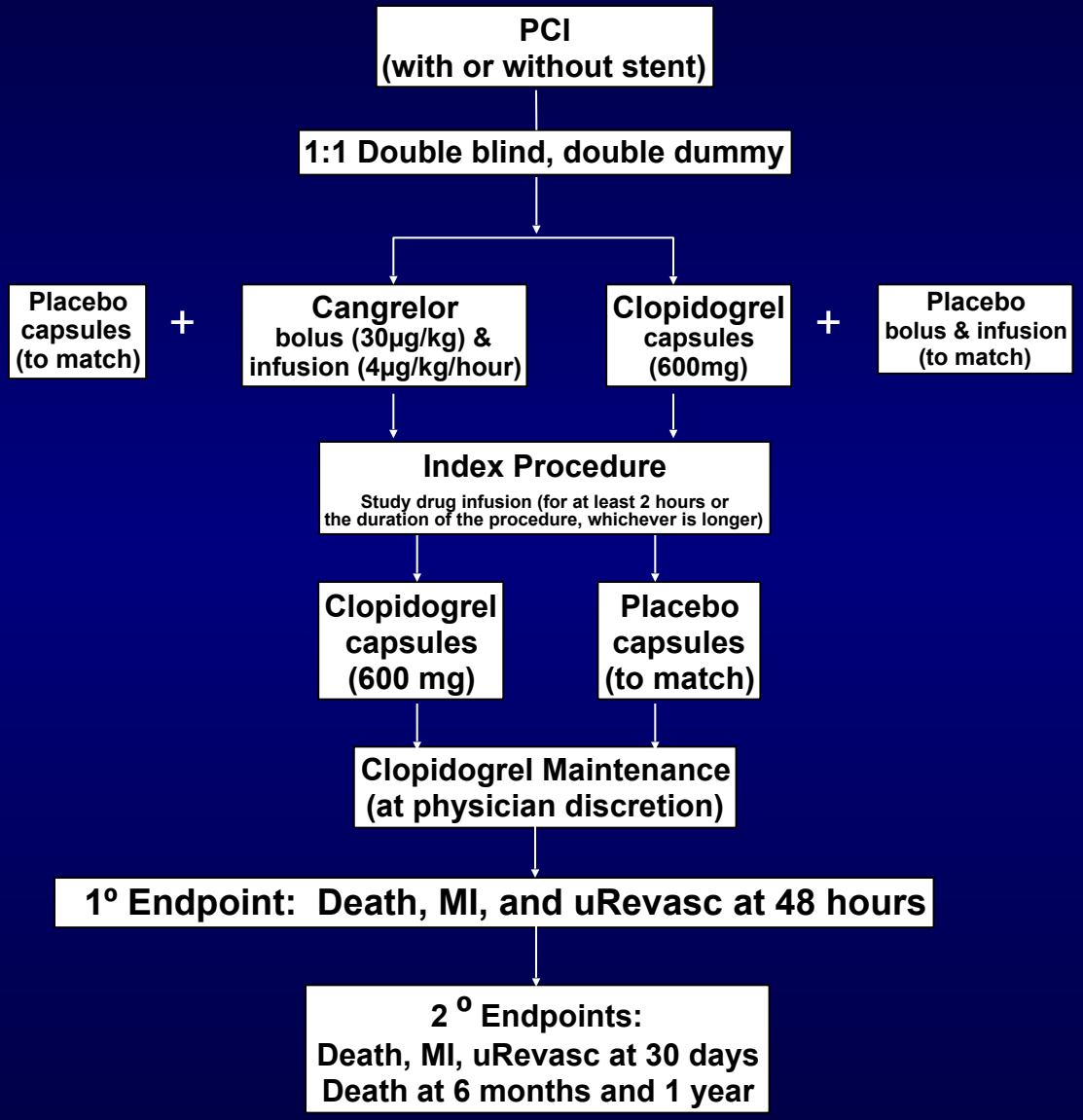
Double-blind randomized trial performed in US



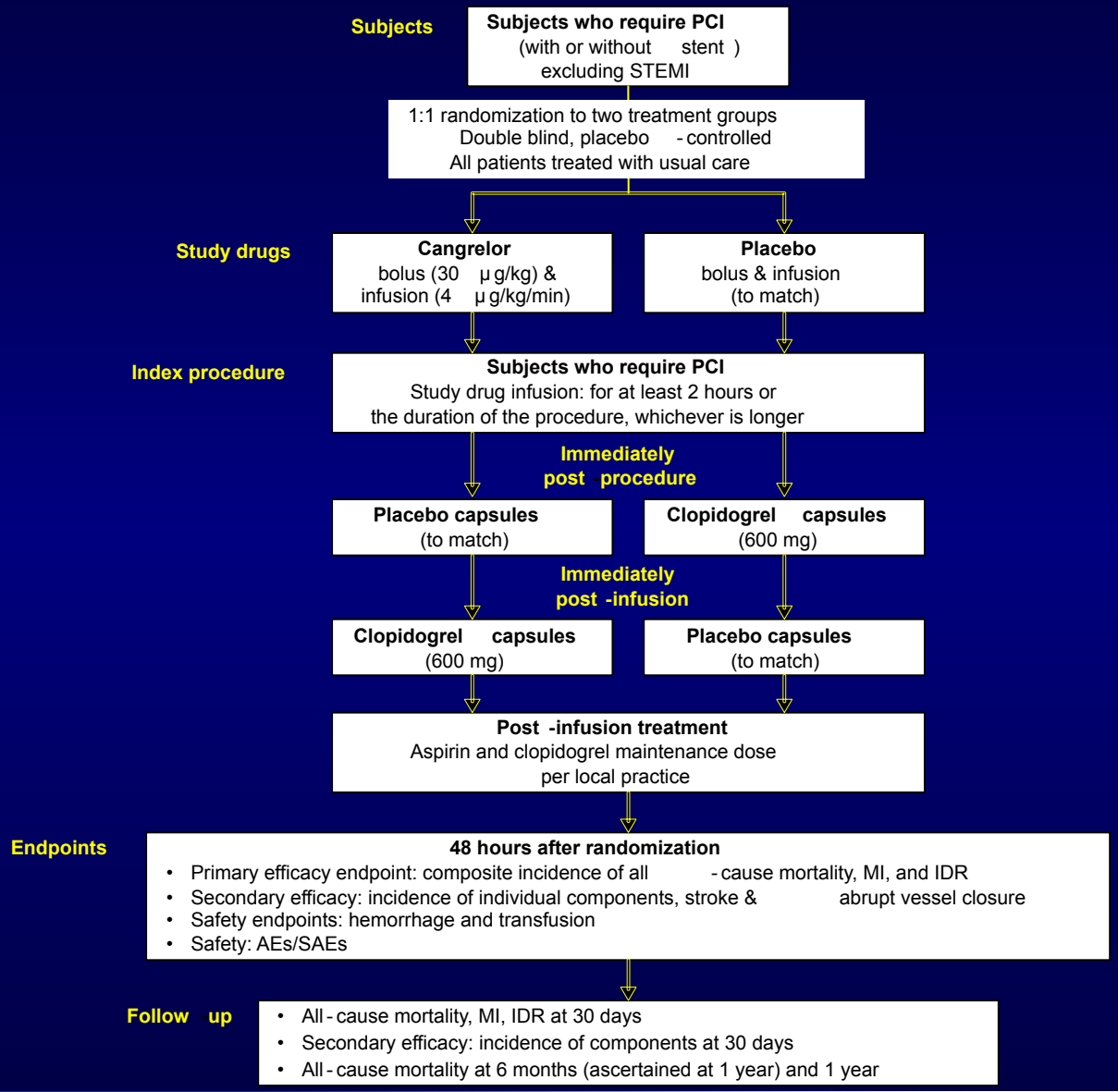
AR-C69931MX report number SC931-5129 Part 2

Greenbaum et al. Am Heart J. 2006;151:689.e1-689.e10

CHAMPION-PCI



CHAMPION-PLATFORM

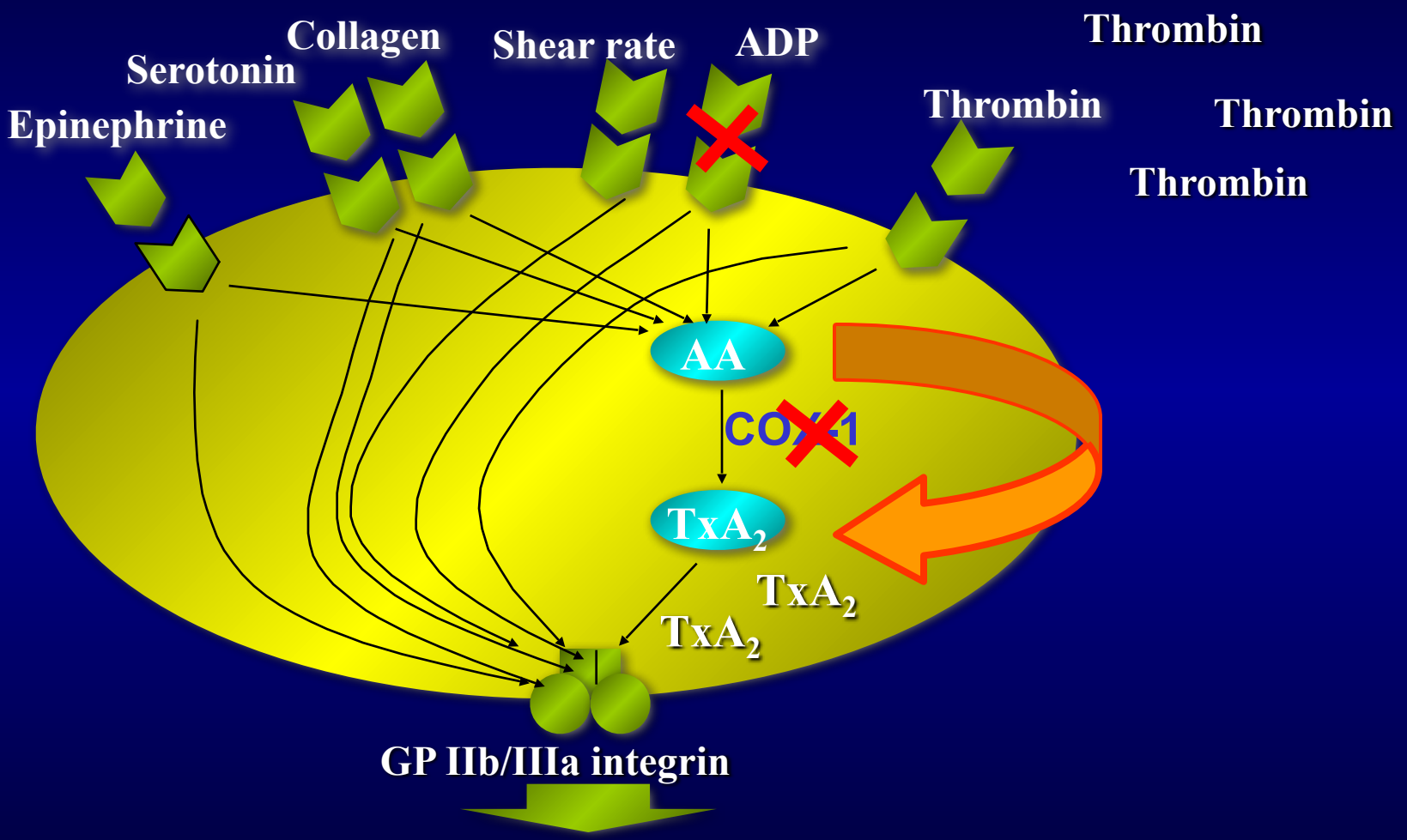


Will New $P2Y_{12}$ Inhibitors Reduce Resistance?

	Prasugrel	Cangrelor	AZD6140
• Rapid onset	✓	✓	✓
• High level of inhibition	✓	✓	✓
• Reversible	✗	✓	✓
• No resistance	☺	☺	☺

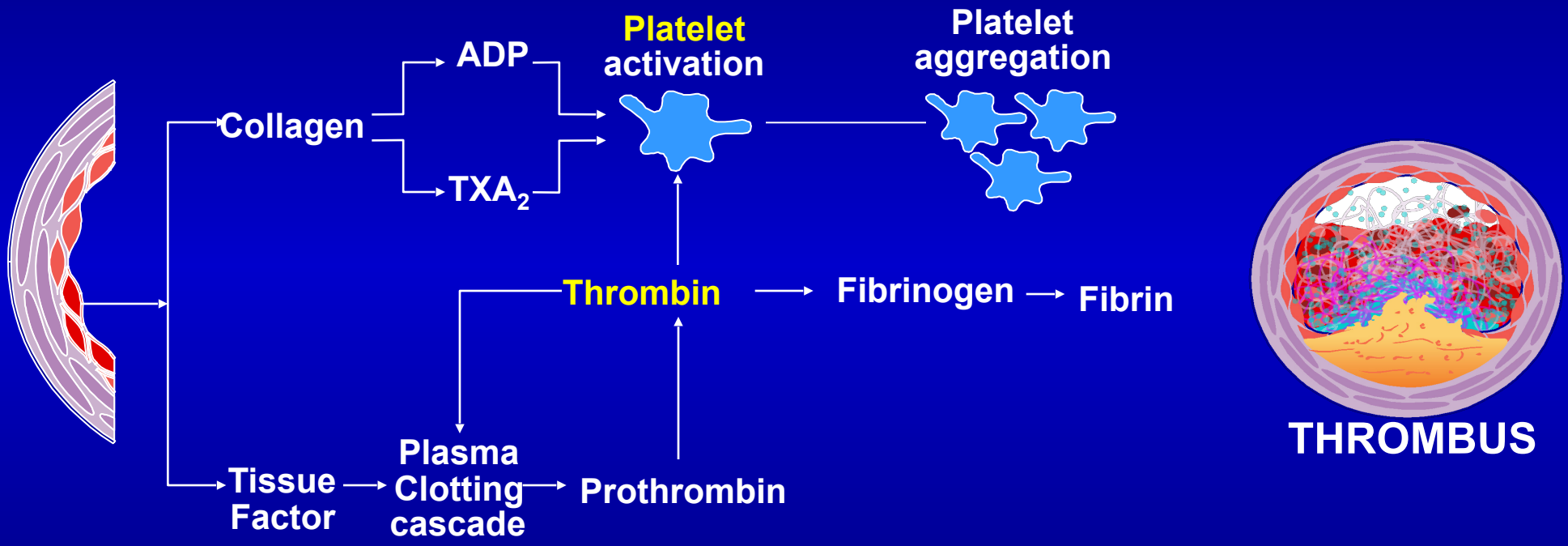
More Potent Clinical Outcomes??? Better Clinical Outcomes!!

Platelet Stimuli

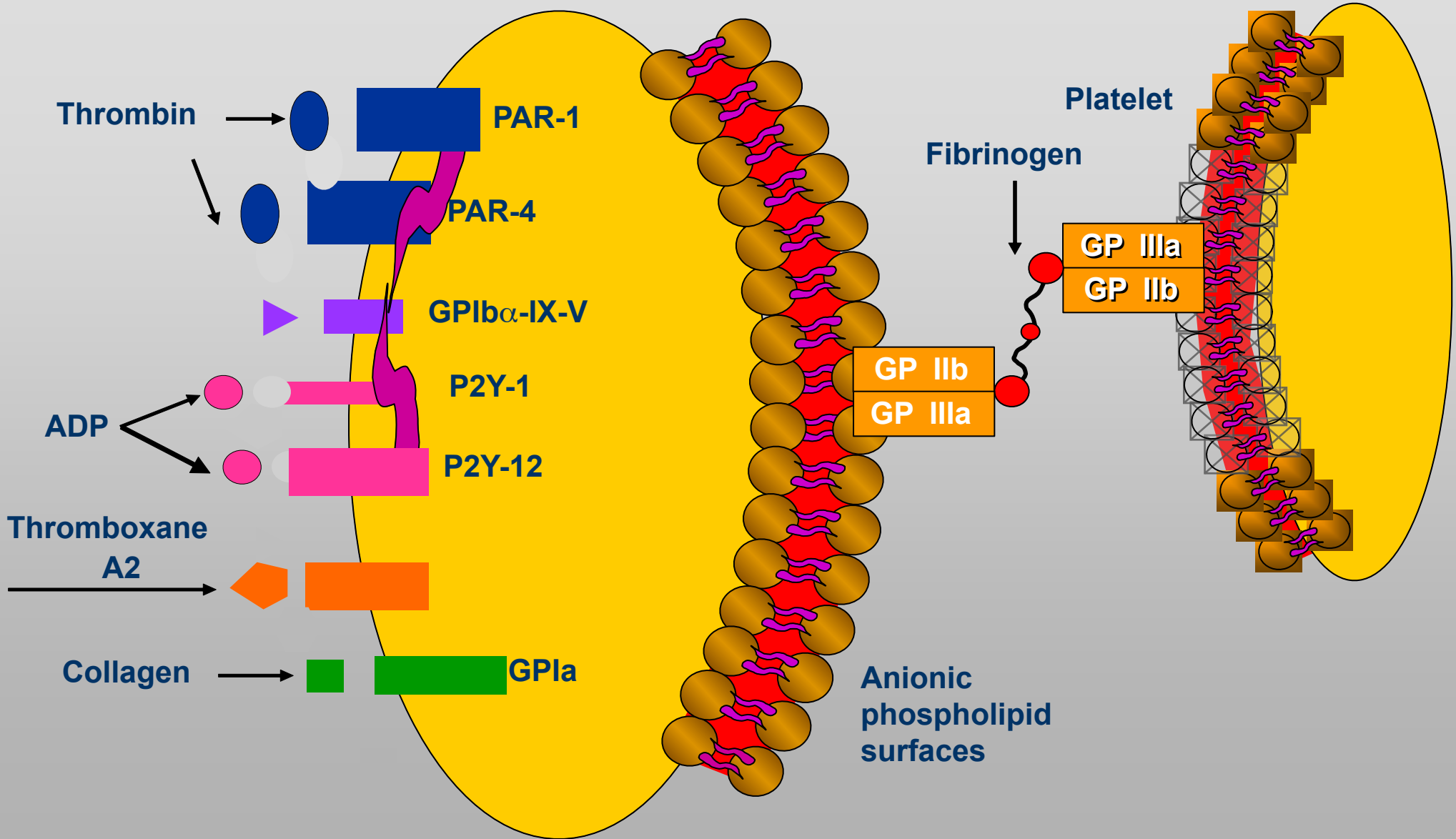


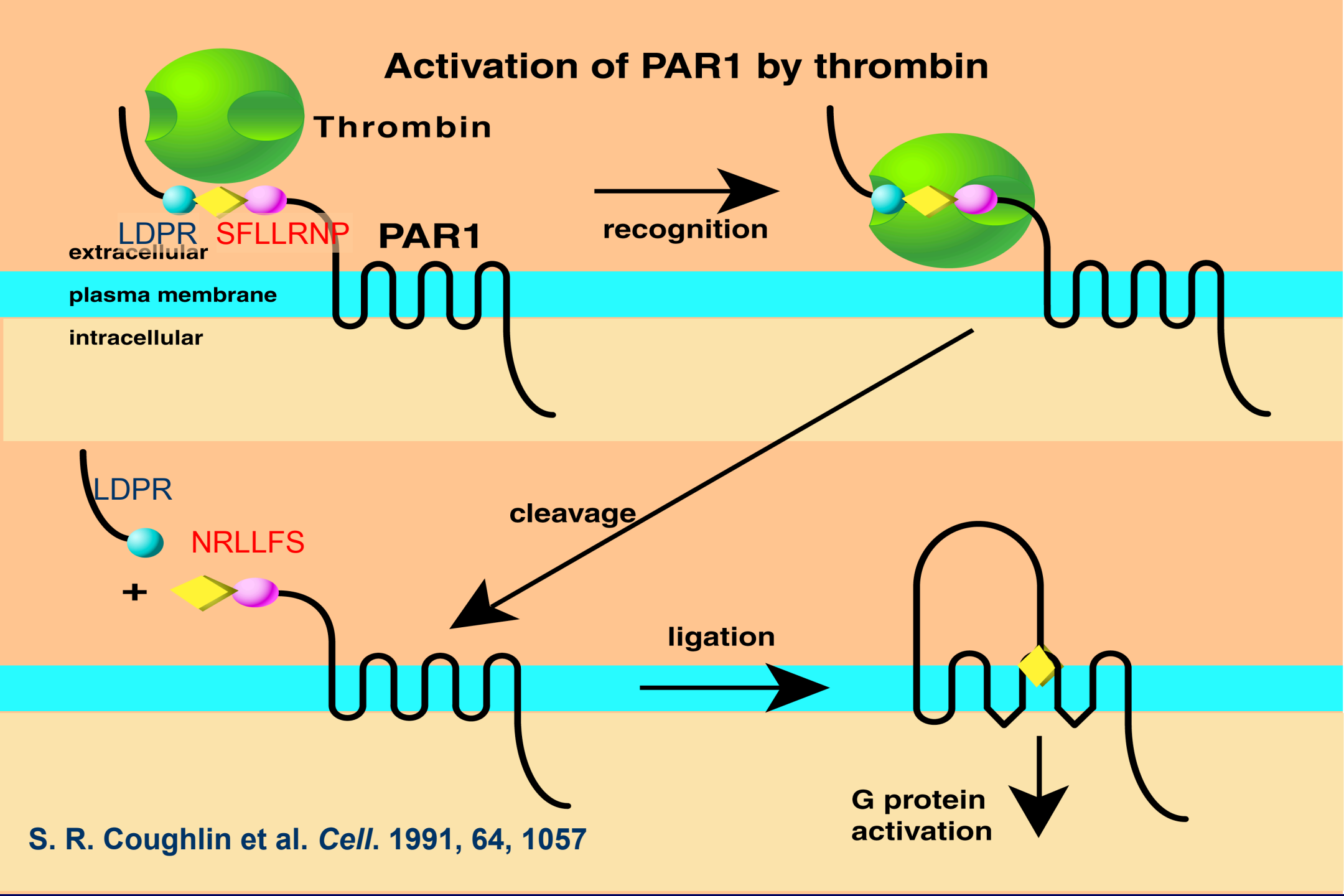
Thrombus Formation

Two key elements: cellular (platelets) and plasmatic (coagulation factors)



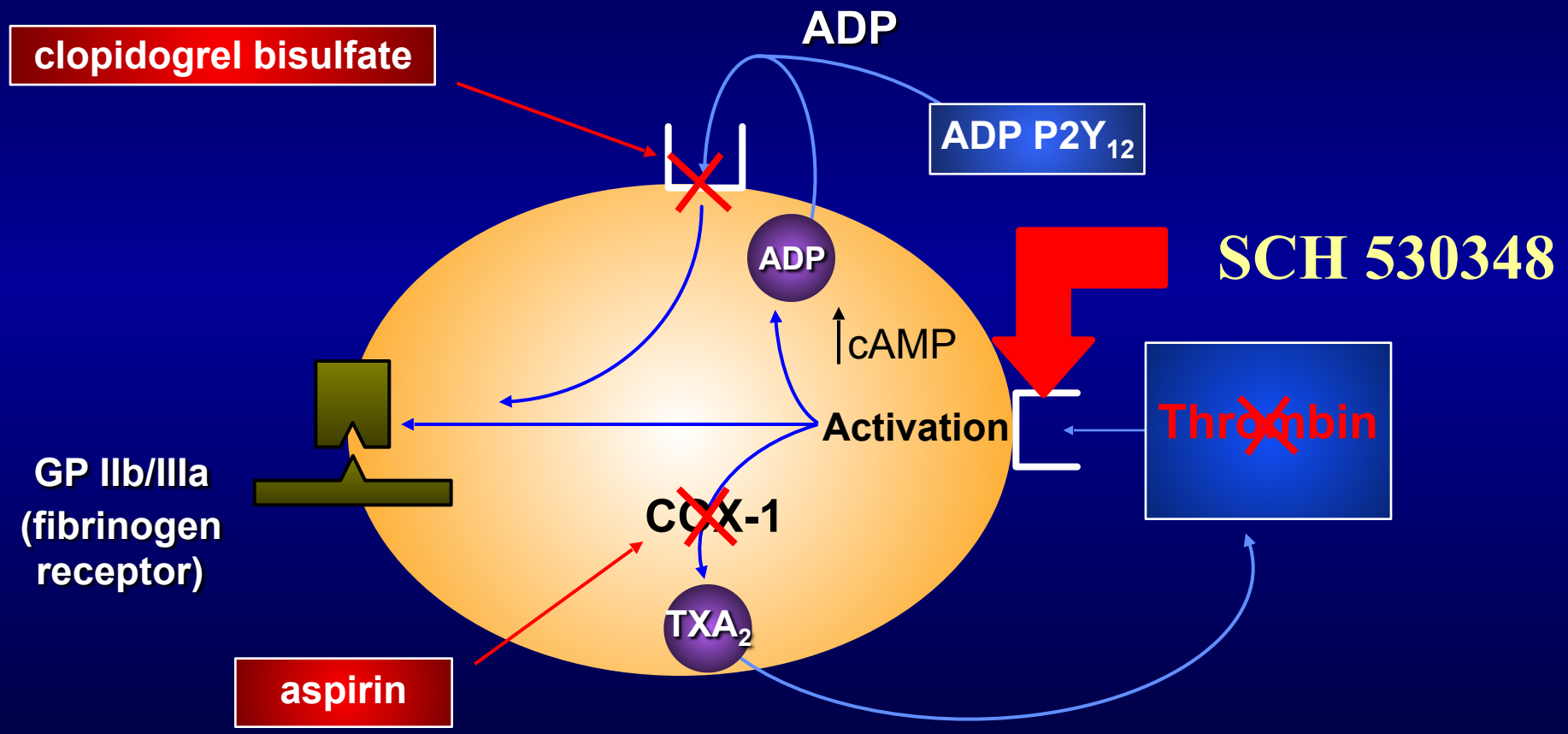
Platelet Receptors




Activation of PAR1 by thrombin
Thrombin
LDPR
SFLLRNP
PAR1
extracellular
plasma membrane
intracellular
recognition
LDPR
NRLLFS
+
cleavage
ligation
G protein
activation
S. R. Coughlin et al. *Cell*. 1991, 64, 1057

Oral Anti-PAR-1 receptors

TRA-PCI trial



adapted from Schafer AI. *Am J Med*. 1996;101:199-209.

T·R·A-PCI Study Design

Non-Urgent PCI or Cath possible PCI (All Receive Aspirin)
Randomization #1 — 3:1 SCH530348:Placebo (Single Loading Dose)
Sequential Groups: 1=10 mg; 2=20 mg; 3=40 mg, or Placebo

Cardiac Catheterization
Planned PCI (All Receive Clopidogrel and Antithrombin)

Randomization #2 1:1:1
Maintenance Therapy Once Daily for ~ 60 days
SCH 530348 Loading Dose → SCH 530348
Or Placebo Loading Dose → Placebo

SCH 530348

0.5 mg n~100	1 mg n~100	2.5 mg n~100	Placebo n~100

Safety: TIMI Major plus Minor Bleeding
Efficacy: Death/MACE

* *Primary Evaluable Cohort*

No PCI**

CABG

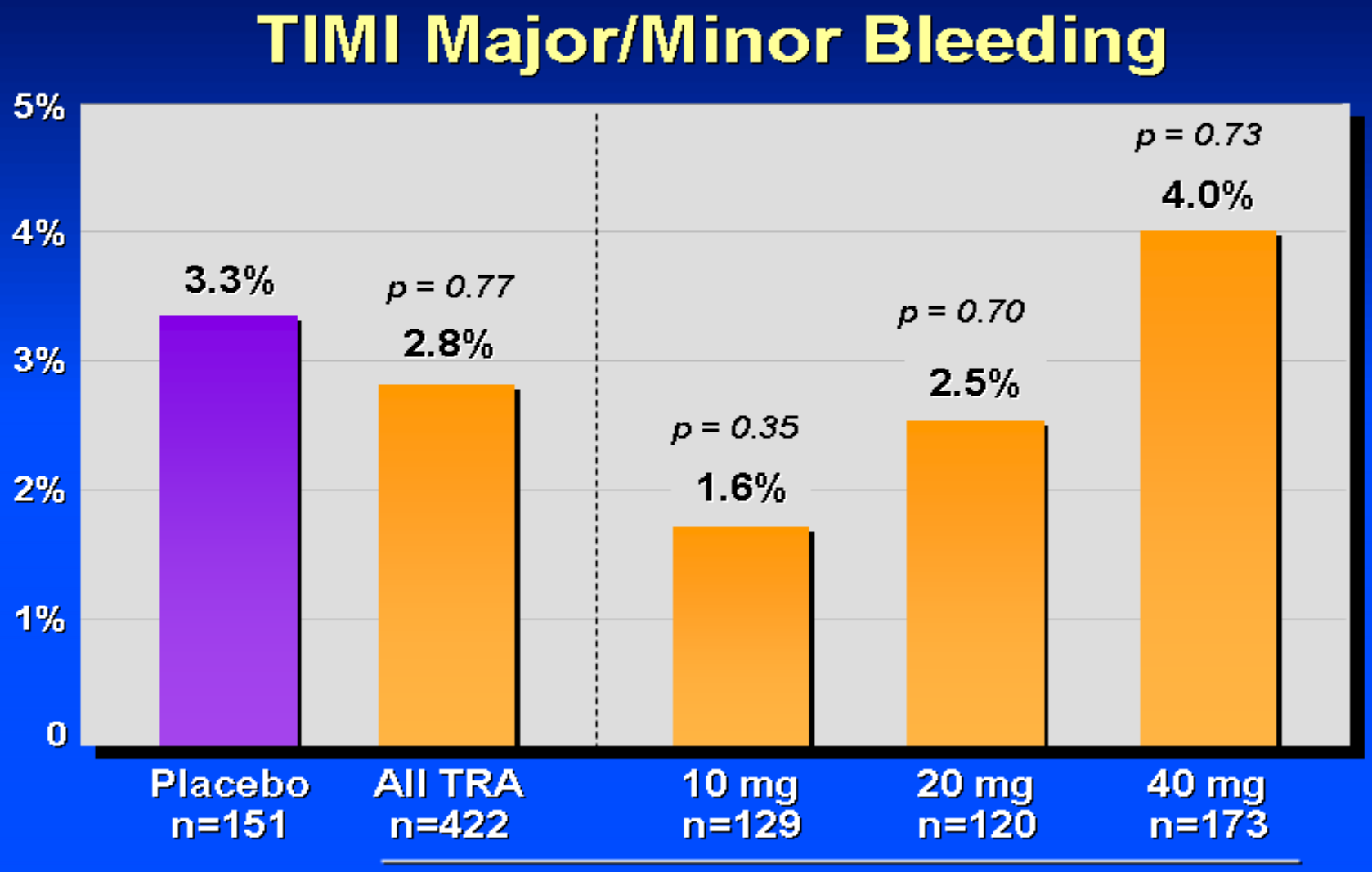
Medical Management

Quantify Postoperative Chest-Tube Drainage, Transfusions, and Re-exploration

Safety: TIMI Major plus Minor Bleeding

***Secondary Evaluable Cohort*

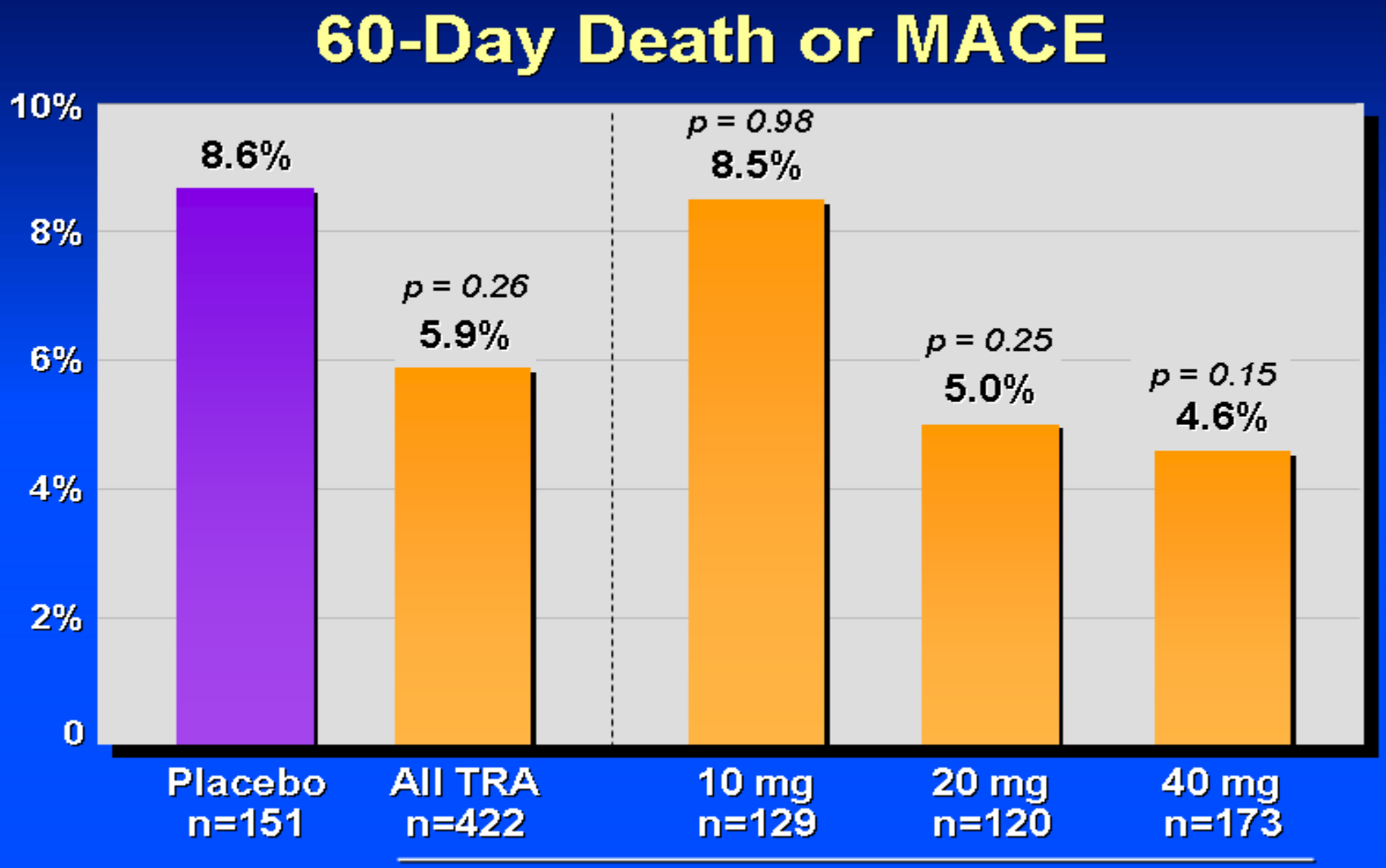
PCI Cohort



p- value relative to placebo

T·R·A-PCI

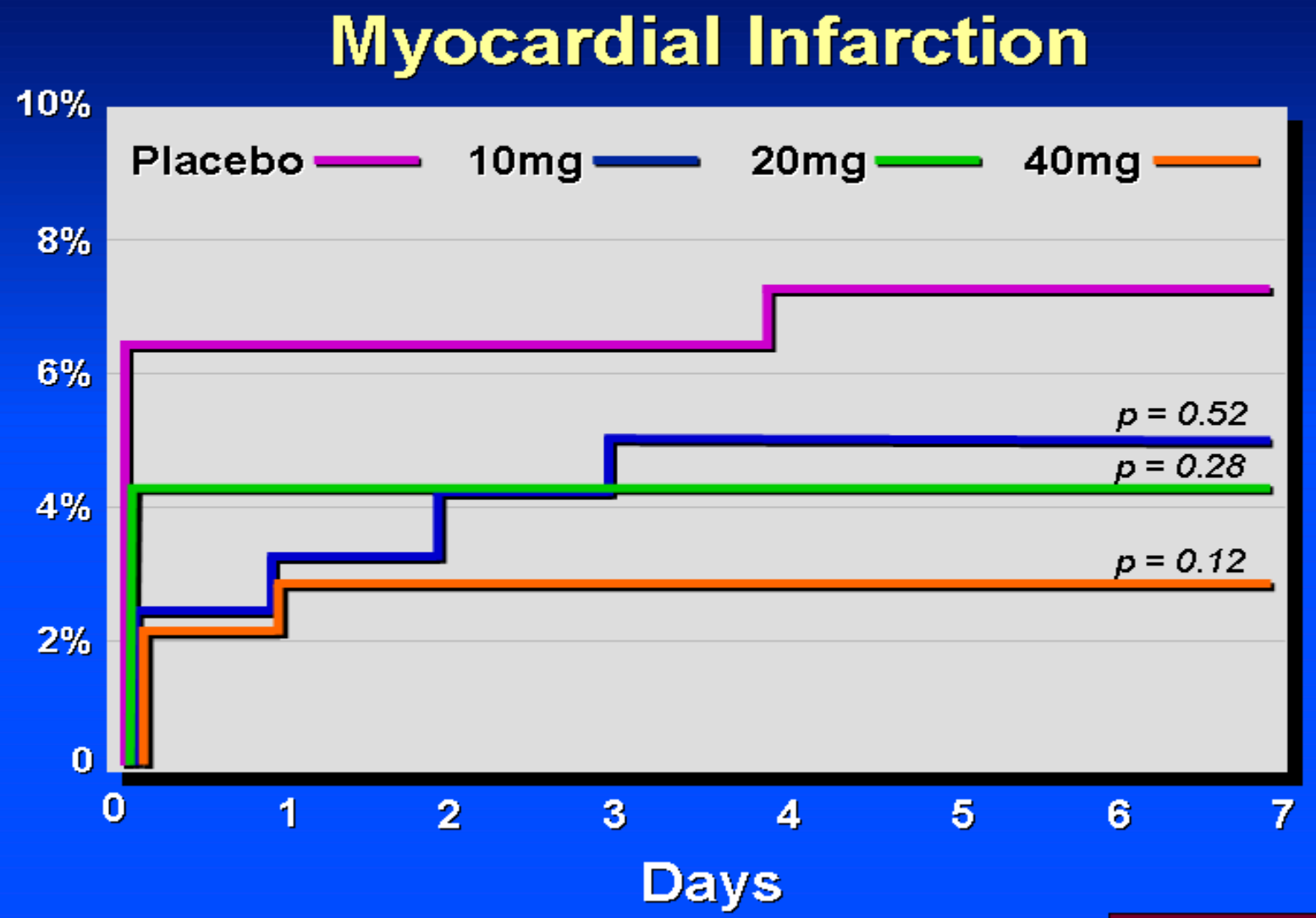
PCI Cohort



p- value relative to placebo

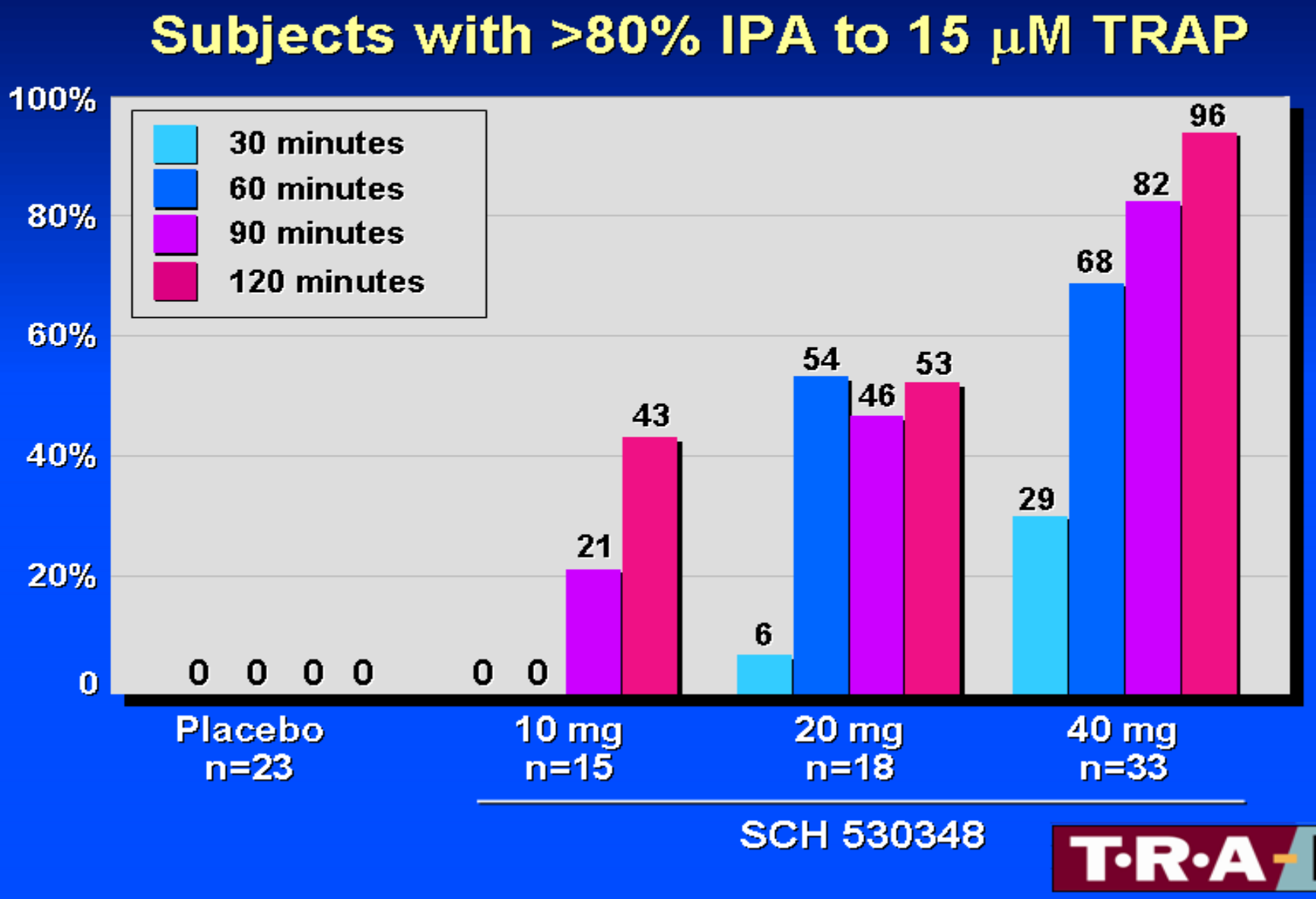
T·R·A-PCI

PCI Cohort



T·R·A·PCI

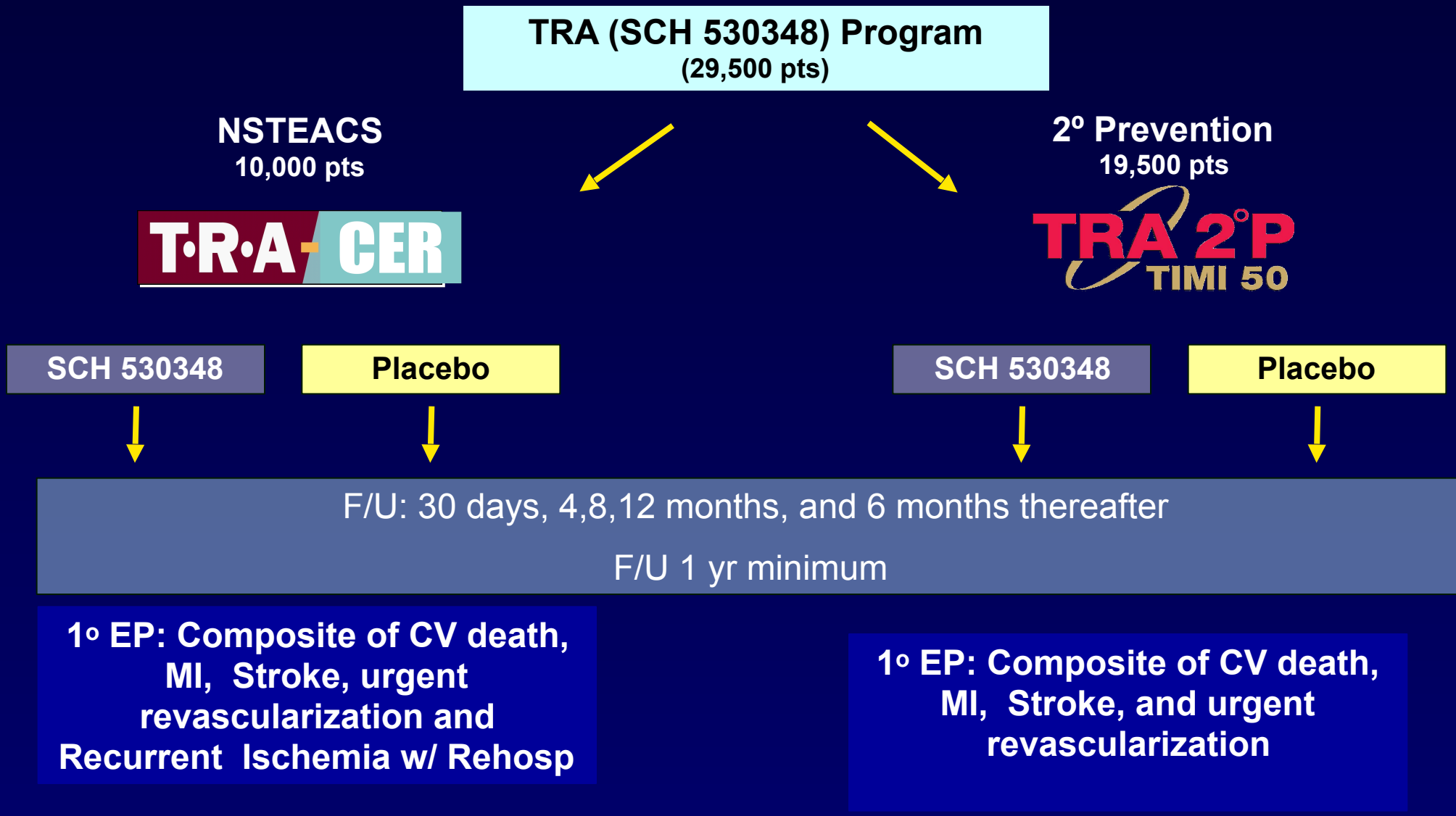
Platelet Aggregation Substudy



T·R·A-PCI

TRA (SCH 530348) Program

Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis



……. to be continued !!!!!!!!!!